Prolonged and Perplexing Fevers

by CHESTER S KEEFER, M D

Physician in-Chief and Director Evans Memorial Massachusetts Memorial Hospitals Wade Professor of Medicine Boston University School of Medicine

and SAMUEL E LEARD, M D

Assistant Visiting Physician and Assistant Member Evans Memorial Massachusetts Memorial Hospitals Instructor in Medicine Boston University School of Medicine



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Preface

One of the problems most frequently encountered in medical practice is the diagnosis of prolonged fever with or without local signs of disease This problem perplexes both the physician and the patient and it has not become less important with the introduction of new agents for the combating of acute infections There continue to be a large number of disorders causing fever which do not respond to any of the known therapeutic agents

A definitive diagnosis of the cause of an obscure or prolonged fever is not always established In some cases the fever subsides after an indeterminate period the patient recovers his health and a diagnosis is never made In others a diagnosis is finally established by the appearance of local signs of disease through biopsy of tissue or by means of surgical operation In a few instances the diagnosis is disclosed at autopsy

The purpose of this book is to present the various means of establishing the diagnosis of prolonged fevers In developing the material and assembling our experience we have confined our attention to those disorders in which fever commonly persists for 2 weeks or longer We have emphasized those cases in which the causes may remain obscure for a long period of time The topics selected for discussion have been arranged in order of importance and frequency

We have drawn also on the experience of DuBois Reimann Alt Barker Kirshner Hamman Wainwright

Beeson, and others who have been interested in this or allied subjects for many years These authorities have contributed greatly to the careful follow up of patients with the diagnosis of fever of obscure cause at the time of discharge from the hospital

Conclusions have been hard to draw, since one is concerned with many of the usual diseases presenting themselves in an atypical manner It is hoped that this presentation will be of value in helping physicians to cope with this problem in a more precise way and on the basis of rational planning

CHESTER S KEEFER M D
SAMUEL E LEARD M D

Boston Massachusetts
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Prolonged and Perplexing Fevers

Introduction

Speaking broadly a prolonged fever is usually found to be caused by *an atypical manifestation of a common disease rather* than by a rare disease It is well to be familiar with the common as well as the rare causes of prolonged fever together with the methods by which one can arrive at the diagnosis so that a plan for diagnostic study may be formulated

One of the early discussions of prolonged fever in the United States was published by Richard Cabot in 1907 under the title of *The Three Long Continued Fevers of New England* In 1911 when he published his two-volume book *Differential Diagnosis* he discussed the causes of long fevers" and short fevers At that time the three commonest causes of long fevers were typhoid fever sepsis and tuberculosis Today the frequency of these three disorders has changed but the causes have not changed appreciably Forty four years ago Cabot pointed out that when studying the obscure fevers of long duration one should search especially for pulmonary and renal tuberculosis typhoid fever hepatic subphrenic renal and perirenal suppurations and vegetative endocarditis He therefore stressed the importance of suspecting the lung the liver the kidney the heart and the blood

Few attempts have been made to follow patients diagnosed as having fever of unknown origin at the time of discharge from a hospital Alt and Barker (*1*) were able to follow 101 of 173 cases so diagnosed at the time of discharge from the Peter Bent Brigham Hospital in Boston between 1913 and

1930. These cases were found in reviewing the records of 34 000 medical patients who entered the hospital during that time. Forty two patients, the majority under the age of 30 years, had fever of less than 10 days' duration and recovered completely. Four of this group subsequently developed organic disease, but the onset was far enough removed to make *relationship to the febrile attack unlikely*. Eighteen other patients in the same age group had fever for more than 10 days (the average was 7 weeks) and were discharged afebrile. One developed phlebitis 1½ years later, *another had a subdeltoid* bursitis 2 years later, and one in whom fever lasted for only 10 days was seen 6 years later with aortic insufficiency, thought to be due to rheumatic fever.

Another group of 18 patients of various ages and with diverse types of fever were hospitalized for an average of 10 weeks and on discharge were still febrile. Eleven remained entirely well for 1 to 10 years. Two had continued fever. Five died 6 weeks to 4 years after leaving the hospital. Two of these were elderly individuals in whom the diagnosis was some type of malignant disease. One had bacterial endocarditis, 1 had some form of sepsis, and 1 died of streptococcal pharyngitis.

One other patient who was described separately was a 17 year-old Armenian-born boy, who was admitted five times within 3 years. Each time he had pain in his abdomen and extremities, which he had had four to six times yearly since the age of 4. Accompanying the pain there was fever varying between 101 and 102°,* and leukocytosis. In 1928 he was still having attacks three or four times a year in spite of splenectomy.

Few patients probably had brucellosis. Another group of patients with afternoon temperatures of 99.6 to 101° were

*All temperatures given in this book are in Fahrenheit.

grouped together They all had easy fatigue weight loss mild joint pains and a tendency to psychoneurosis or vasomotor disturbances Another case was reported to have been diagnosed later as paratyphoid fever

The last group of 23 cases in which an ultimate diagnosis was established included 3 cases of pulmonary tuberculosis 1 of miliary tuberculosis 1 of tuberculosis of the cecum 1 of tuberculosis of the Fallopian tubes 6 of rheumatic carditis 1 of generalized carcinomatosis 1 of carcinoma of the stomach 1 of carcinoma of the esophagus 2 of lymphoblastoma 1 of aleukemic leukemia 1 of hyperthyroidism and 1 of psoas abscess One patient was relieved by appendectomy 1 responded to antisyphilis therapy and 1 responded to antimalaria therapy

In brief among the cases studied by Alt and Barker which were followed for a sufficient period of time to establish a diagnosis, the cause of the protracted fever was found to be tuberculosis a tumor or rheumatic fever There were a few cases of undulant fever and a few with septic infections In a number of cases the cause of the fever was never established

Kintner and Rowntree (*2*) reviewed the Mayo Clinic records from June 1919 to June 1930 and analyzed 100 records They excluded patients under 15 years of age and all those who had chills In the group reviewed fever and symptoms had persisted for at least a month prior to registration at the clinic The cause of the fever was undetermined Fifty five of these patients continued to have fever In the entire group focal infection was found in 35 cases and in only 60 per cent of these had the fever subsided Seven patients all over 44 years of age died Three of these cases were diagnosed at autopsy as streptococcal septicemia, vegetative endocarditis and sarcoma of the kidney In 1 case a mass had

developed in the right upper quadrant and in the 3 others the cause remained undetermined

In this group then the cause of the fever remained unsolved in most cases Septic infection and tumors were the two diagnoses established at autopsy in several patients Focal infection appeared to play very little part in the clinical features of the disease

Hamman and Wainwright (*3*) studied 90 cases and recorded the results Thirty six patients had long-continued low grade fever In 10 of these characteristic signs or symptoms developed which made diagnosis possible in 18 symptoms disappeared slowly as the febrile state subsided in 8 symptoms and fever persisted for many years and a diagnosis was never made in spite of careful observation and painstaking examinations Of the 10 cases in which an accurate diagnosis was made 3 were brucellosis 2 pulmonary tuberculosis 2 hypernephroma 1 Hodgkin s disease 1 ureteral stricture and 1 tertiary syphilis

In 54 cases there was protracted high fever In the 44 cases which were finally diagnosed the commonest causes were tuberculosis septic infection or a tumor These diagnoses included 2 gonococcal septicemia 1 perirenal abscess 1 liver abscess 1 perisplenic abscess 10 syphilis 9 tuberculosis 4 Malta fever 1 tularemia 1 typhoid fever 1 malaria 1 amebiasis 4 Hodgkin s disease 5 hypernephroma 1 carcinoma of the lung 1 carcinoma of the liver and 1 sarcoma of the spleen

Keefer (7) pointed out that all physicians are familiar with the instances of fever which subsides after a period of time without a diagnosis ever being made and which may be classed as "pyrexia of unknown origin" He gathered 80 cases that he had seen in 8 years in which the cause of fever was eventually determined. Of these cases in 51 fever was due to

specific infections in 10 to tumors in 9 to disease of the blood forming organs in 7 to disorders of the heat regulating mechanism and in 3 to cirrhosis of the liver (See Table 1)

TABLE 1

CAUSES OF PROLONGED FEVER IN 80 CASES

Specific Infections				51
Tuberculosis			8	
Mediastinum		3		
Pericardium		3		
Lymph nodes		2		
Abdomen	1			
Chest	1			
Streptococcal			10	
Endocardium		4		
Mediastinum		2		
Spleen		2		
No focus		2		
Staphylococcal			6	
Bones		1		
Muscles		3		
Mastoid		1		
Kidney		1		
Undulant fever			6	
Bones		1		
Iliac artery		1		
No focus		4		
Typhoid paratyphoid fever			2	
Kidney		1		
Spleen		1		
Meningococcal sepsis			2	
Gonococcal sepsis			2	
B tularensis			1	
E coli			4	
Liver		2		
Bile duct		2		

TABLE 1 (*continued*)

Rheumatic fever		4	
Dysentery		1	
Amebic infection		1	
Periarteritis		2	
Lupus erythematosus		2	
Tumors			10
Stomach		3	
Cancer	2		
Leiomyosarcoma	1		
Colon		3	
Pericolic abscess	2		
Cancer without abscess	1		
Liver		1	
Kidney		3	
Diseases of Blood Forming Organs			9
Lymphoma		5	
Hodgkin's disease	4		
Myeloma	1		
Infectious mononucleosis		2	
Abdominal form	2		
Aplastic anemia		1	
Aleukemic leukemia		1	
Disorders of Heat Regulatory Mechanism			7
Hyperthyroidism		2	
Habitual hyperthermia		4	
Heart failure		1	
Cirrhosis of Liver			3

PART ONE

Regulation of Temperature and Diagnostic Studies

CHAPTER I

Variations in Normal Body Temperature

It is known that Hippocrates was aware of fever and of its importance as a prognostic sign In 1625 Sanctorius (*4*) began estimating the temperature of the human body In 1852 Traube (*5*) published the first temperature curve to appear in the medical literature He persuaded Wunderlich to study the subject and the result was Wunderlich s classic monograph which appeared in 1868 (*6*) His thermometer was 1 foot long and had to be held in the axilla for 20 minutes DuBois (*7*) while attending Spanish American War soldiers became interested in the study of heat production and heat loss and his studies have led to many outstanding advances

Before attempting to evaluate the normal variation in body temperature, we shall review briefly the conditions and changes in daily life which produce it The factors involved include the time of day when the temperature is taken (diurnal variation) the age of the patient whether exercise preceded the measurement the time of the last meal emotional factors whether or not the patient is pregnant change in posture the time of the last menstrual period if the patient is a female and the state of hydration It is evidently essential to make sure under what conditions the temperature was taken before attempting to evaluate a single reading



clared that rectal temperatures averaged 0 18 to 1 8° higher than oral Hewlett (*12*) recorded differences of 1 0° Burton Opitz (*13*) stated a difference of 0 54 Howell (*14*) agreeing with Pembrey declared the average oral temperature to be 98 36° and the average rectal temperature to be 98 96°

MacLeod (*15*) tells us that the rectal temperature is 1 8° higher than the oral temperature Wright (*16*) believed the rectal temperature to be 0 5 to 0 75° higher and realized that the difference was increased with exercise

Carmichael and Linder (*17*) studied the oral and rectal temperatures in 24 normal active males The mean oral temperature was 97 93° and the mean rectal temperature was 98 88°, a difference of 0 95° In a group of 25 hospitalized schizophrenic males the difference was only 0 54°

In short there is general agreement that the rectal temperature taken under basal conditions — that is without previous exercise — will vary from 0 5 to 1 0° higher than a properly recorded oral temperature This difference should be taken into account in considering slight variations in normal body temperature

Bardswell and Chapman (*18*) found the rectal temperature to be 1° higher than the axillary at rest and 2° higher after exercise

DIURNAL VARIATION

Bardswell and Chapman (*18*) reported observations on 7 males and 2 females between 20 and 35 years of age whose average temperature between midnight and 4 A M was 96 8° on waking 97 8° at 10 A M 98 4 and between 11 A M and 6 P M (usually 4 to 6 P M) 98 4 to 98 8° Sahli (19) pointed out that the minimal temperature occurred within a few hours after midnight, with the first max

imum during the forenoon and a second maximum between 5 and 8 P M Liebermaster (quoted by Sahli *19*), in a study of active normal persons found a variation of 1 8° during a 24 hour period and one of 0 9° between morning and afternoon temperatures

Lyon and Wallace (*20*) reported on 250 hospitalized patients The mean axillary 7 A M temperature was 97 2° (±0 004) and at 7 P M it was 97 45 (±0 006) The average daily temperature was 97 32° They concluded that the temperature of hospitalized patients was 1° less than for ambulatory patients

AGE

Children have a more fluctuating temperature than adults Williams (*21*) checked the temperature of 254 active British elementary school children not suspected of having pulmonary tuberculosis rheumatism or tonsillitis and found oral temperatures of 98 6° or below in only 29 5 per cent In contrast to this study Paton (*22*) investigated 108 boarding school girls 12 to 17 years of age and concluded that the normal temperature was nearer 97 4° than 98 4° He believed that an oral temperature of 98 4° was suggestive of illness

Ivy (*23*) recorded the temperatures of 276 medical students while they were in class after breakfast between 8 and 9 A M He found a range of 96 5 to 99 3° with a mean oral temperature of 98 1° Sixty-eight per cent (±1 S D from the mean) had a temperature range of 97 3 to 98 5°

EXERCISE

It has been known since the middle of the nineteenth century that muscular activity increases temperature Bardswell

and Chapman (*18*) stated the difference to be 0 9° at rest and 1 8° immediately after exercise

Carmichael and Linder (*17*) mentioned exercise as a factor in influencing temperature but gave no specific data

EATING, POSTURE, PREGNANCY, HYDRATION

Other factors which should be considered in the taking of the temperature include the time of the last meal Horan (*24*) stated that with eating there can be a temperature elevation of 0 5 to 1 0 Another determination which is not well documented in the literature is the effect of posture It is also thought that there is an increase in temperature from the basal level after the first trimester of pregnancy

The hydration state of the tissues is important in determining body temperature Thus patients who are dehydrated may have an elevation of temperature which returns to normal after proper fluid balance has been established The correction of this factor helps to differentiate quickly between fever from infection and from dehydration alone

OVULATION

The fact that the body temperature varies during the menstrual cycle has been known for many years Tompkins (*25*) stated that body temperatures taken daily under standard conditions show a typical curve during the first part of the month drop to a minimum about the time that ovulation occurs, and rise definitely thereafter to a relatively high level which is maintained until the next menses when the temperature drops abruptly If the temperature shows a rise of two or three fifths of a degree and if this rise corresponds with a similar

one in the previous menstrual month and is not due to other illness it can be assumed that ovulation is occurring

The usual pattern consists of a low temperature in the range of 97° followed by an abrupt rise to as high as 99 3° In one patient followed by Reimann the cycles of fever have recurred with the menstrual cycle for 32 years

PSYCHOGENIC FEVER

The body temperature is extremely labile in some persons and may be elevated by emotional stimuli Patients frequently show a transitory elevation in temperature soon after admission to a hospital This increase is probably due to the exercise involved in coming to the hospital together with the excitement and anxiety involved in leaving the usual environment This subject is discussed in more detail in another section

Reports on fever in children due to emotional upset are frequent in the literature Baldwin (26) reported on 5 infants admitted to the Bellevue Hospital in New York who had no disease but ran persistent fevers for several months The infants were admitted because their mothers were ill or were otherwise unable to care for them The interval between admission and the onset of the fever varied from 7 to 18 weeks Usually the temperature was between 101 and 103°, but in 1 case it rose to 107° The children did not appear to be acutely ill They were usually pale apathetic, uninterested in their environment, and unresponsive Their weight was stationary The most striking feature of the report was the prompt defervescence which took place when the patients were returned to their homes Repeated outpatient hospital visits resulted in consistently normal temperatures Other reports of fever in children from emotional upsets have been

described by Pototsky (*27*) Horder (*28*), and Chapin (*29*) Another reference on the subject is by Bakwin (*30*)

Wynn (*31*) reported the average temperature of 324 subjects undergoing draft examination as 99 3° Two-thirds of the men had temperatures above 98 6° He also checked the temperature of 40 persons taking state board examinations Their average temperature was 98 9° before the examination and 98 3° after it

In the vast majority of patients with psychogenic fever the temperature does not rise above 100° The circumstances under which the observations are made are very important in assessing the significance of slight temperature elevations

HABITUAL HYPERTHERMIA

A few cases of prolonged fever have been reported in which the body temperature is elevated to 99 8 or 100 0° (usual range 98 6 to 99 8°) for periods varying from 1 to 19 years The temperature rises following exertion or emotional strain and in the latter half of the menstrual cycle No other cause of the fever is found Many of these patients are made chronic invalids Some of them are sent to tuberculosis sanatoria Others are considered to have undulant fever

Falcon Lesses and Proger (*32*) described the case of a 20 year-old Italian woman who on twenty nine visits to the outpatient department had an oral temperature ranging from 99 6 to 100 5° The pulse rate was usually elevated When she was purposely frightened by the suggestion of an operation her temperature rose from 98 2 to 99 0° After a 10 minute vaginal examination her temperature which before the examination had been 98 8° rose to 99 7° The authors considered that the patient was definitely not psychoneurotic,

and believed that psychic stimuli and thermoregulatory mal adjustment were the etiologic factors They pointed out that Dejerine recognized fever of short duration occurring in neurasthenia associated with emotional stimulation and that Osler also differentiated clearly between hysterical fever with moderate and with extreme elevations

Reimann (*33*) reported 16 cases with prolonged subfebrile temp-rature rarely exceeding 100° All the patients were women and 10 were unmarried Two general types emerged 5 patients had no complaints and were regarded as healthy, 11 were regarded as neurotic and had a multitude of bizarre complaints for which no cause could be found after prolonged search with all the diagnostic methods available Of interest was the frequency of low basal metabolic rates which were not influenced by thyroid medication In 1 patient pow dered opium was given with cessation of the fever during the time the drug was active, aminopyrine had no effect on the temperature The sedimentation rate in this group of patients was generally within normal limits

Wolf and Wolff (*34*) described a case of recurrent high fever with a benign outcome occurring in a patient with mi graine They pointed out that in 1914 Friedmann and Kohn stamm (*35*) recognized that fever frequently accompanied excitement and emotional tension in the absence of physical overactivity Eichelberg (*36*) was able to induce temperatures up to 102 5° in patients under hypnosis Dejerine (*37*) wrote that temperature elevations might readily be attributed to emotional causes in the absence of demonstrable physical disea e

The case reported by Wolf and Wolff had been previously reported by Scott and Kirschner (*38*) and by Allen (*39*) At the time of admission to the New York Hospital the patient was 43 years old His father had suffered from similar attacks

of headache and fever between the ages of 25 and 40 with spontaneous recovery A sister and aunt had had migraine headaches The present illness started during late adolescence with periodic headaches characterized by bifrontal pain and pain in the eyeballs photophobia and nasal discharge which were frequent at the time of emotional strain At the age of 31 the patient suddenly ceased having headaches and began experiencing recurrent attacks of fever malaise and aches and pains in the back and extremities He felt well again within 2 days The second attack came on 6 weeks after the first In 12 years the attacks had become more frequent occurring weekly at the time of admission to the hospital The patient had prodromal symptoms for about a day with aches and pains in the ankles and spine a feeling of mental unrest and difficulty in concentrating Fever often had its onset with a shaking chill The white cell count would rise to 15 000 Aspirin and aminopyrine could lessen attacks but could not prevent them Intravenous typhoid vaccine would alter the timing of the fever There was no weight loss or debility

There had been a period of 100 days after 5 years of fever during which there had been a remission of fever but headaches recurred While being studied at Stanford University the patient had received x ray therapy to the cervical lymph nodes Glyceryl trinitrate and sodium nitrate had aborted two attacks but had no effect on a third attack

After admission to the hospital a personality study was performed during which a great many disorders were uncovered with the ventilation of conflicts During this regime the patient s fever stopped and he had neither fever nor headaches for almost a year He had recurrence only under unusual tension Wolf and Wolff therefore believed that the fever was due to a temporary derangement in the thermoregulatory

and believed that psychic stimuli and thermoregulatory mal adjustment were the etiologic factors They pointed out that Dejerine recognized fever of short duration occurring in neurasthenia associated with emotional stimulation and that Osler also differentiated clearly between hysterical fever with moderate and with extreme elevations

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The normal subjects showed very little change in temperature while the hyperthermic patients exhibited an average increase of 0 7° There was also an increase in the pulse tremor and localized perspiration The same number of patients were given citrated caffeine Three of the 4 hyperthermic patients had an average rise of temperature of 0 4 There were changes of pulse tremor and perspiration similar to those noted in the hyperthermic patients receiving amphetamine sulfate Three hyperthermic patients were given scopolamine hydrobromide subcutaneously without any change in temperature but with a decrease in s veating Similar results were obtained with atro pine Two patients were given morphine without any change in temperature pulse tremor, or localized sweating Five pa tients were given 10 grains of potassium bromide orally for 9 days without appreciable effect The same was true with 1 grain of sodium amytal given orally three times a day for 7 days Five hyperemic patients and 5 normal subjects were given 10 000 000 killed typhoid organisms intravenously with tempera tures taken every 2 hours for 12 hours The normal subjects showed an average rise of 1 while the hyperemic patients had one of 3 8°

During an exciting card game 3 patients had an average rise of 1 5 while the normal subjects had a rise of 0 1 to 0 2° During the showing of a battle film 5 hyperemic pa tients had an average rise from 99 0 to 100 3° During a dull moving picture the same group had a fall of temperature from 99 1 to 98 8° Three hyperemic patients were told that their cases were to be reviewed for return from overseas Their temperature rose from an average of 99 4 to 100 5° when they appeared before the disposition board Three pa tients with infections were checked under similar circum stances and had an average rise of 0 3°

PERIODIC FEVER

Among the cases of periodic fever reported by Reimann and deBardinis (*41*) was that of a 50 year old woman who at the age of 37 began to have attacks of chills, fever nausea, and pain in the abdomen chest, and extremities The attacks lasted 5 to 7 days and recurred every 17 to 22 days with no relation to the normal menstrual cycle Porphyrin studies showed no evidence of fluctuation from normal

A man with recurrent weekly attacks of fever and abdominal pain was placed on an elimination diet without improvement An electroencephalogram showed no evidence of abnormality

A physician had attacks of abdominal pain fever, and leukocytosis at intervals of 1 week to 1 month These were similar to the periodic attacks of abdominal pain in a 17 year-old Armenian boy reported by Alt and Barker (*1*) Other cases reported by Reimann included that of a man with cyclic neutropenia and ulcers in the mouth occurring at 21 day intervals a woman with episodes of arthralgia in the joints at intervals of 14 days and a patient with periodic myasthenia who eventually died of pneumonia

Reimann s new cases of periodic fever included some more very interesting unexplained ones The first was that of a 42-year old Negro who had chills nausea headache and fever every 6 weeks and later every 4 weeks The temperature on admission to a hospital was 104° and the pulse was 120 After numerous tests a clinical diagnosis was made of brucellosis military tuberculosis Hodgkin s disease or other lymphoma The patient left the hospital apparently well but returned with a recurrence in 3 weeks A few months later he was admitted for the third time with a temperature of 105° and tachycardia of 150 complaining chiefly of weakness and

pains in the calves The severity and duration of attacks had increased lasting for 10 days There was albuminuria The Bromsulphalein liver test showed 18 per cent retention Aminopyrine reduced the temperature to normal on two oc casions Twenty-eight days later the patient had another at tack and was admitted to another hospital where his temper ature was 105° Penicillin was given without effect After 10 days of fever the temperature returned to normal on aminopyrine During the next episode the patient died suddenly in another city No autopsy was obtained

A 17 year-old boy who had had hay fever for 10 years had a family history of allergy Red swellings 2 to 3 cm in diameter appeared transiently over the body and face oc casionally accompanied by redness and swelling of the pha ryngeal joints These attacks ceased 6 months later In the meantime an attack of fever to 104° occurred lasting an hour and causing profuse sweating dull frontal headache and stiffness of the arms and legs lasted for 24 hours The pa tient was thereafter well until another cycle recurred in 14 days Thereafter the episodes took place every 2 weeks with an increase in the headache During one attack a shaking chill was noted

Eight months later the patient was hospitalized Two days later a predicted episode occurred but examination revealed only warmth and tachycardia of 130 An excised lymph node showed chronic lymphadenitis The white cell count during the fever was 11 800 with 98 per cent neutrophils after the episode the count was 4600 with 43 per cent polymorphonu clear leukocytes The sedimentation rate by the Cutler method was 15 mm in 35 minutes After two similar episodes the number of leukocytes fell to less than 5000 per cubic millimeter A tuberculin test caused no reaction The basal met abolic rate during an episode was —8 per cent and in fever free

periods —20 and —33 per cent Six units of crystalline insulin given intravenously caused mild hypoglycemic symptoms in 15 minutes without evidence of other endocrine dysfunction Further endocrine studies failed to reveal any specific abnormalities The patient was started on 50 mg of testosterone propionate given intramuscularly twice weekly The height of the fever declined the bouts of fever were of shorter duration, and there was a decrease in the severity of symptoms According to Reimann this improvement was coincident with testosterone therapy but it is doubtful whether it was caused by the drug When last heard from about 6 months later the patient was having bouts of stiffness of the arms and body and low grade fever every 2 or 3 weeks

A 50 year old married woman had menopausal symptoms for several months after a hysterectomy and oophorectomy The symptoms began with a shaking chill lasting for 30 minutes This subsided without other symptoms The next week headache began It started in the evening and was followed by a chilly sensation during the night with the temperature often reaching 104° The episode lasted for 24 hours and was followed by a period of relative comfort for 24 hours after which another attack occurred This cycle continued and malaria was therefore suspected but quinine quinacrine hydrochloride sulfonamide and penicillin had no effect on the febrile periods The attacks persisted causing a loss of 22 pounds in 4 months Six months later therapy with estrogen was begun and continued for a year The afebrile intervals gradually increased to 3 or 4 days The attacks were not so severe as the earlier ones but lasted for 48 hours The next year the patient was given pamaquine quinacrine hydrochloride and quinine again without effect The cycles lengthened to 7 days The gallbladder was removed about 33 months after the onset of illness During convalescence the febrile episodes were milder recurring about

every 7 days but later they became as severe as before Antipyretic drug provided transient relief

There was no evidence of allergy or other disturbances The white cell count during one episode was 11 500 with 56 per cent neutrophils In January 1949 the patient was still having febrile episodes between 5 and 7 days apart

Another intere ting case was that of a patient who was stud ied over a 30 year p^riod At the age of 3 she had had pain in the abdomen chills and fever which occurred after a large meal and la ted for a day Thereafter similar attacks recurred at intervals of approximately 2 weeks The tonsils were re moved without any effect on the attacks At the age of 9 the patient had an attack characterized by chilline s fever rising to 104° and pain in the abdomen The symptoms lasted for 24 to 48 hours Leukocytosis as high as 37 000 occurred during the attacks Her appendix was removed without effect At the age of 12 fever occurred between 4 and 8 days apart The Wassermann reaction was positive Two years later the cerv ical lymph nodes were swollen and the patient jerked and twitched in a manner suggestive of chorea or hysteria A sec ond tonsillectomy was performed without effect Soon after ward both shoulders and one knee hurt during the febrile bouts and the white cell count numbered 13 000 to 15 000 The Wassermann reaction was negative At that time because of itching of the conjunctivae preceding the attacks an al lergy was suspected Fever was occurring every 6 days at this time

On different occasions during the following years the pati^nt was given various elimination diets and was kept in a room with filtered air There was never any eosinophilia At the age of 9 fever occurred with attacks between 4 and 8 days apart Three years later it occurred every 2 or 3 days in the fol lowing year at 4- to 20-day intervals and 5 years later at 4

to 35 day intervals At home episodes occurred about every 2 weeks At one time she was free of fever for 3 months Throughout her course she had innumerable laboratory studies and many consultations without fruitful results At the age of 33 a normal gallbladder with a few stones was removed Three years later the patient had no episodes during the last 7 months of a normal pregnancy At the age of 40 she was having two types of attacks One was characterized by chills fever and abdominal pains The other was described as arthralgia with temperature elevation to 104°

A 68 year-old woman had episodes of fever, malaise and arthralgia for over 20 years Antimalarial therapy was of no avail The episodes at first occurred every 28 days and later every 14 days Fever of 102° lasted from 2 to 3 days and was reduced by salicylates

A 54 year-old man had febrile episodes three or four times a year consisting of severe chills lasting an hour, followed by fever to 103° Severe sweating followed with complete recovery after 12 or 15 hours During the next 2 years the episodes occurred at shorter intervals Intensive therapy with penicillin sulfonamides and streptomycin gave no relief In 1946 the attacks increased in severity and the duration was 36 to 72 hours Chlorguanide hydrochloride an antimalarial drug was given without improvement At the time of Reimann s report the attacks were still occurring every week to 10 days Sometimes the episodes began without chills but fever headache and perspiration were constant lasting for 5 to 6 days

Another patient had bouts of fever for 5 years characterized by pharyngeal injection backache headache generalized muscular pains fever to 102° and severe prostration lasting 6 to 7 days The attacks occurred regularly every 6 or 8 weeks The leukocytes numbered from 8000 to 10 000 The spleen had

been palpable during each attack since 1946 All studies for malaria were negative In May 1947 an attack seemed to be terminated by penicillin therapy and there was no recurrence until May 1948

A 28 year old man had had episodes of chills and fever since the age of 10 months During childhood they recurred at 6- week to 2 month intervals and lasted for 3 days to 2 weeks For the last 5 years the attacks had recurred every 6 months On admission to a hospital the patient had shaking chills a temperature of 105 and tachycardia There was a faint systolic apical murmur The white cell count was 7000 Malarial parasites were not seen

In 1949 Brick (*42*) reported the case of a 41 year old man with periodic episodes characterized by fever chills and my algia beginning at the age of 29 Episodes recurred three or four times a year and later every 3 or 4 weeks The temperature reached 104 or 105° with drenching perspiration headache anorexia nausea and occasional vomiting The patient was hospitalized sixteen times but numerous tests failed to reveal the cause of the attacks Sulfonamides antibiotics blood trans fusions tonsillectomy exploratory laparotomy and appendec tomy were carried out without effect There was leukopenia of 3000 with 28 per cent neutrophils The eosinophil count fell from a total of 122 prior to the attack to zero during an episode

Reimann s reports included the case of a 13 year-old boy who had had attacks since the age of 2 characterized by upper respiratory symptoms dermal eruption diarrhea stiffness of the muscles stupor and signs of disturbance of the central nervous system Later there was fever to 104° The white cell count sometimes reached 18 600 The mother and two cousins had allergic disorders

THERMOREGULATORY FUNCTION OF THE CENTRAL NERVOUS SYSTEM

The central nervous system plays a very important part in the temperature regulation of the human body The hypothalamus is probably the control point and is affected by afferent impulses from the heat and cold receptor centers of the skin Also the temperature of the blood supplying this part of the brain causes possible modification in efferent stimuli which control the vascular bed of the skin

Keller and Hare (*43*) confirmed the work of Isenschmid and Schnitzler (*44*) Their observations indicated that the chief central mechanism controlling heat production is located in the hypothalamus and that extirpation of this region releases the heat loss mechanism located elsewhere, from co ordinated control

It has been known since 1922 that in midbrain preparations rabbits have an absence of heat regulation Keller and Hare (*43*) studied 30 midbrain preparations of rabbits Shivering was never observed it was necessary to keep the animals in an incubator to obtain normal body temperatures hyperthermia from central trauma meningitis or infections of the peritoneum or lungs was never observed sweating never resulted even when the temperature reached 110°, typical panting was seldom observed

Of 10 medullary preparations only 4 were maintained more than 2 days postoperatively Shivering was readily elicited, normal temperatures could be maintained in unheated cages, and hyperthermia was observed in 2 instances where lesions were highly traumatic Heating of animals led to slower respiration Sweating was not observed.

Magoun *et al* (*45*) activated the heat loss mechanisms by local heating of the basal ganglia Direct heating and cooling

had inverse effects on body temperature There appeared to be a left ganglia dominance of this phenomenon

There have been reports of brain tumors which affected the temperature of the body This subject is discussed in Chapter V

Heating and cooling carotid artery blood have been shown to have a direct effect on body temperature probably due to the effect on the hypothalamic center

Wilder (*46*) discussed the subject of fever from the stand point of central nervous system disease He cited 4 cases of meningococcal meningitis in children who had only mild toxicity and fever without any localizing signs He pointed out that in encephalitic patients fever headache and drowsiness may be the only signs or symptoms Syphilitic meningitis may present itself as a fever About 30 per cent of these cases have a negative blood serology Wilder also included chronic brain abscess trauma to the midbrain scurvy causing intracranial hemorrhage hemorrhage aneurysm or thrombosis of the midbrain and brain tumors of the midbrain as causes of fever of central nervous system origin with few localizing signs Damage to the cortex by intravenous arsenicals methyl salicylate and lead should also be included in the possible causes of obscure fever

In summary the literature has shown rather conclusively that there is a heat regulating center in the brain which plays an important part in body temperature regulation When this center is interfered with by tumor infection toxic agents, or vascular insufficiency fever of obscure origin may result.

NEUROGENIC HYPERTHERMIA

Neurogenic hyperthermia is manifested by a high internal temperature and a cold dry skin occurring shortly after head

injury or operation in the region of the third ventricle or pos terior fossa, and less frequently with tumors in the diencephalon The patient is unconscious the respiratory and pulse rates are usually very high and the outcome is fatal

Body temperature is the algebraic sum of the functions of the heart and general circulation of blood of the general metabolism of the cutaneous vasoconstriction and vasodilatation and of the rapidity of respiration For this reason manifestations of neurogenic hyperthermia may vary inasmuch as variable por tions of the neural centers and pathways directly or indirectly concerned with heat regulation are affected by the lesion Er ickson (*47*) has reviewed the subject of neurogenic hyperthermia

HEAT LOSS THROUGH THE SKIN

As has been shown by many investigators including DuBois (*7*) the body temperature is controlled by two factors heat production and heat loss One of the major avenues of heat loss is through the skin When a naked man is exposed to an atmos phere of 72° there is a constant loss of heat through the sur face of the skin which assumes an average temperature of 86° Th s means that there is a gradient from the interior of the body to the surface averaging 1 8 to 2 5 cm in depth The temperature of the extremities owing to their location is un der cool conditions considerably below that of the largest part of the body

The body has an excellent system of controlling the blood flow to the surface Under cool conditions it is possible for the skin to act in the same way as clothing These changes are reg ulated by sense organs for heat and cold which are located in the skin

There are four means of heat loss from the skin radiation

convection conduction and vaporization Radiation is pro portional to the temperature of the surface of the body minus the temperature of the surrounding objects or air multiplied by the surface area corrected for the character of darkness of the surface The human body is within 1 to 2 per cent of being a perfect infrared black body radiator

Convection is directly related to the movement of air It in creases with acceleration of air movement up to about 70 miles an hour Vaporization depends on the difference between the vapor pressure of the air immediately in contact with a slightly moist skin and the vapor pressure of water in the surrounding air (humidity) Under ordinary conditions about two-thirds of the water vaporized from the body comes from the surface of the skin Vaporization accounts for about 25 per cent of heat loss at 68° All methods of heat loss are proportional in some way to the total surface area or more properly profile surface area

Another minor means of heat loss from the skin is conduction which takes place when one lies on the cold ground or touches a cold metal object

Chills are possibly mediated from the thermal receptors in the skin When the average body temperature drops two thirds of a degree chills occur with surprising regularity This reaction can be delayed by the ingestion of brandy and produced more rapidly by the drinking of ice water At the time shivering starts oxygen consumption increases

Ordinary clothing does not change the fundamental concepts regarding the proportions of heat lost by the various channels but it does extend the comfort zone into the colder region

Fever Due to Changes in the Skin There are several conditions causing obscure fever in warm environments which bring out the importance of heat loss through the skin The first

of these is hereditary ectodermal dysplasia of the anhidrotic type Sunderman (*48*) referring to the previous reviews summarized the salient features of this entity as the absence of sweat glands and occasionally lacrimal glands the growth of a scanty fine lanugo type of hair the total absence or incomplete development of teeth and the presence of chronic rhinitis frequently associated with loss of the sense of smell

The chief complaints of these patients were fever and headache when they were exposed to high temperature Some patients including 2 of Sunderman s were advised to enter tuberculosis sanatoria because of a positive Mantoux test and fever The nail bed capillaries were increased in number Biopsy of the skin revealed a total absence of the apocrine (sweat) glands These forms were highly developed with hypoplasia of the involuntary muscles in the surrounding area

Sunderman found that these patients may have a rise of 2° in body temperature after exercise after ingestion of hot drinks, or on being wrapped too warmly Exposure to heat increases the rate of respiration a result similar to the panting of dogs Insensible perspiration also causes some loss of water In a warm environment the skin is dry and velvety Diuresis is also observed on acute exposure to a warm environment

In any patients with obscure fever it is well to keep ectodermal dysplasia in mind since it is known that some people sweat only unilaterally There may be some patients with only a partial ectodermal dysplasia which has not been recognized

Another condition which indicates the importance of the skin in relation to heat loss and regulation of body temperature is tropical anhidrotic asthenia O Brien (*49*) recently studied 38 typical severe cases The usual history is that after a few months in the tropics the patient develops malaria which may not be severe After a short latent period exhaustion headache dysp-

nea and giddiness are noted while the patient is working in the heat The skin is dry (anhidrosis) and a gooseflesh like rash may be seen It is generally agreed that all un blocked sweat glands hypersecrete during the course of the disease In O Brien s cases fever between 100 and 102 6° was noted

Another condition which relates the skin to temperature ad justment in a warm environment is seen in patients who have had sympathectomies performed for hypertension and have high fevers on hot days during the summer months In the sympathectomized areas there is an absence of sweating

Two cases of general acquired anhidrosis have appeared in the literature This condition is the sudden total disappearance of ability to perspire Fog (*50*) reported the case of a man who had a long febrile illness diagnosed by Widal agglutinations as paratyphoid fever Within a month after returning to work he noted inability to perspire With exposure to heat or with ex cessive exercise he had attacks of general indisposition pre cordial pain palpitation dyspnea and a feeling of skin con gestion Diuresis was increased Biopsy of the skin showed that half of the sweat glands had undergone degeneration Pharmacologic and physical tests verified the anhidrosis The patient was observed for over 2 years without the occurrence of change

Engelhardt and Melvin (*51*) reported the case of a 49 year-old woman with a chief complaint of fever and burning of the skin For 13 years she had noted nervousness dyspnea and a feeling of increased body heat with temperatures up to 102° orally occurring only in the summer Her temperature and de gree of discomfort were directly proportional to the environ mental temperature In youth she had had typhoid fever Pre viously she had been treated for psychoneurosis Histologically her skin showed generalized atrophy and hyperkeratinization of

the epidermis with focal variations in degree Sweat collected in a room at 120° and 75 per cent humidity represented water lost as a result of diffusion With the administration of pilocarpine there was sweating only in the axillae the per ineal region and to a slight extent over the sternum The patient was followed for 2 years without observation of change

In the differential diagnosis one hould be cognizant of a case reported by Berkman and Horton (52) Between the ages of 11 and 26 this patient lived in a basement in the summer due to inability to adjust to heat During the following 9 summers she worked as a camp counselor At the age of 36 she was seen at the Mayo Clinic with a chief complaint of intolerance to heat since the age of 11 She stated that at an environmental temperature of 85° she became dyspneic and unable to walk be cause of weakness Frequently it took 2 to 3 months to regain her strength Following subcutaneous pilocarpine generalized light sweating was observed She was observed again the next year and her walk suggested hysteria She was induced to sit in the sun and on the fourth day generalized perspiration oc curred Following discharge from the hospital she had no fur ther symptoms even when the environmental temperature reached 110° Berkman and Horton felt that her condition suggested temporary dysfunction of the sympathetic nervous system

Obscure fever has also been ascribed to ichthyosis (Woodyatt 53) Other skin changes which may influence heat loss are those seen in scleroderma and in myxedema

These cases indicate that fever may be due to the patient s in ability to lose heat through his skin by means of vaporization An inability to perspire easily such as is seen in congenital and acquired anhidrosis may account for an elevation of tempera ture following exercise or in warm environment

HEAT LOSS THROUGH THE LUNGS

The lungs are important in the heat loss of the body mainly in the evaporation of water by this route According to Du Bois (7) about one third of the water vaporized from the human body is from the respiratory tract Another but less im portant cause of heat loss is the warming of inspired air

When the skin is deprived of its ability to lose heat because of abnormalities in the skin there is a compensatory rise in the respiratory rate in order to increase vaporization of water from the lungs It should be remembered that for every gram of wa ter vaporized 0 58 calorie is withdrawn from the body through the latent heat of vaporization

ENVIRONMENTAL FACTORS

Hyperthermia and Heat Stroke Man s survival and work ing efficiency in hot climates or under hot environmental condi tions are dependent on a physiologic adaptation This can be summarized as a combination of decrease in heat production and an increase in sweating When the body temperature reaches a certain critical level just below 102 work becomes inefficient and hyperthermia threatens

Persons working in a hot climate or in a hot environment in industry become physiologically acclimatized This adjustment is marked by a progressively smaller rise in body temperature as one performs a standard piece of work until people com pletely acclimatized are able to work for long periods of time without a rise to the critical level provided the intake of salt and water is adequate

Probably the greatest single factor in producing hyperthermia is the environmental temperature High humidity has been stressed by some authors (54 55 56 57 58) However me

teorologic data derived from a study of heat waves in Massachusetts by Shattuck and Hiferty (*59*) failed to reveal unusual humidity or low wind velocity as a major factor when the heat stroke incidence was the highest The length of time one is subjected to heat and the fluid and salt intake are the chief factors in the production of heat stroke under high environmental temperatures Other factors to be considered include the type and amount of work done the type of clothing worn the diminished resistance to heat after middle age eating and drinking habits and any associated debilitating diseases

In hot climates some men are known to excrete over 9 5 liters of sweat during a work period On the basis of 5 liters of sweat to 42 5 Gm of salt established by Hibbard (*60*), this means a salt loss of nearly 81 Gm

Clinical Syndromes There are three distinct clinical syndromes related to excessive environmental heat cramps exhaustion and stroke Heat cramps are often seen in miners and soldiers in the tropics and are related primarily to salt deficiency The illness is characterized by severe muscular cramps often spasmodic and excessive sweating The body temperature remains normal Symptoms can be relieved or prevented by the ingestion of adequate amounts of sodium chloride The mortality from this condition is negligible

Heat exhaustion on the other hand is manifested by peripheral circulatory collap e (profound sweating pallor of the skin and low blood pressure) The body temperature may be subnormal normal or slightly elevated The characteristic symptoms are weakness dizziness and fainting but nausea and vomiting may also be present

Heat stroke is a much more serious condition than either cramps or exhaustion with a mortality of 10 to 80 per cent in most reported series It has been described in the following

terms sunstroke heat collapse thermal fever and heat hyper pyrexia The outstanding clinical feature is a markedly elevated temperature

In a series of 44 patients in Ohio in the heat of the summer of 1936 reported by Ferris *et al* (*61*) the temperature was below 106 in only 9 patients and in 35 it ranged from 106 8 to 112 A constant finding was the absence of sweating described by some authors as exhaustion of the sweat glands A maculopapular rash was present in 23 patients There was no evidence of congestive heart failure which had previously been reported in the literature In 7 of the 34 patients whose blood pressure was taken on admission the pressure was low and the pulse was weak There was evidence of hemoconcentration as indicated by an elevated serum protein and a rise in hematocrit There was no constant change in the serum chloride blood carbon dioxide content or total serum sodium in relation to the serum protein Acidosis was noted and was attributed to the accumulation of nonvolatile metabolic acids probably lactic acid which is secondary to the high body temperature The arterial oxygen content was normal The clotting time was normal in all patients even those having a purpuric skin rash

Wright *et al* (*62*) discussed the purpuric manifestations of heat stroke seen in 12 patients Wilson and Doan (*63*) had reported decreases in prothrombin and platelets in patients subjected to artificially induced fever The prothrombin deficiency was thought to be secondary to liver damage and the degree of thrombopenia depended on the extent of megakaryocytic damage Wright and his co workers concluded that hemorrhagic phenomena associated with heat stroke in their cases were due to an increase in capillary porosity and a decrease in prothrombin and/or platelets They agreed with Wilson and Doan that the prothrombin deficiency was secondary to hepatic damage and thought that large amounts of menadione administered par-

enterally in addition to early transfusions of whole blood were indicated early in heat stroke to prevent or retard hepatic damage They believed that this might lessen the mortality of those patients who survive the first few hours of hyperpyrexia

The danger of hepatitis in heat hyperpyrexia or induced hyperthermia has been recognized for many years The first symptom is usually exaggerated nausea and vomiting occur ring within 24 hours after the maximum temperature Within 48 hours the urine becomes dark and jaundice becomes ap parent This is followed by discomfort in the upper quadrant of the abdomen and tenderness of the liver In induced hy perthermia recovery is usual in about a week Bragdon (*64*) reviewed the theories of etiology He pointed out that Brown thought inadequate replacement of salt and water was the re sponsible factor MacDonald (*65*) concluded that sulfonamides in fever therapy given for gonorrhea played a major role In the past the activation of a virus has been speculated upon as re sponsible based on the finding of inclusion bodies in the livers of patients coming to autopsy However it is known that in clusion bodies are not specific for virus infection Bragdon thought that the most likely cause of the liver necrosis was the high fever

Hartman and Major (*66*) submitted a group of dogs to controlled fever of 107 and 110 for 5 to 7 hours A constant finding in the animals sacrificed was congestion and hemorrhage in the liver In some of the animals there was extensive mid zonal necrosis of the liver Rawlinson and Kellaway (*67*) perfused cat livers and found that at 104 8° damage was produced uniformly for 6 hours

In the Malamud *et al* (*68*) series of 125 heat stroke victims who died in the army 12 had necrosis of the liver

As to cardiac damage which results from excessive environ mental temperature Wilson (*69*) made a report of 4 fatal cases

1 patient died after sunstroke and 3 patients died after induced pyrexia All the patients had previously been well All showed subendocardial ecchymotic extravasations combined with bloody emphysema of the large bronchi of the lungs The fatal mechanism was thought by Wilson to be the result of a rather extensive hemorrhage under the endocardium on the septal wall in the region of the bundle of His In none of these cases were gastrointestinal hemorrhages found as had been seen in the cases reported by Chunn and Kirkpatrick (*70*)

Logue and Hanson (*71*) in an article on electrocardiographic changes following heat stroke reported the case of a 27 year old soldier who after playing volley ball had a fever of 109 and was irrational The electrocardiographic changes observed resembled those seen in pericarditis associated with bradycardia Within 2½ months the electrocardiogram reverted to normal

SUMMARY AND CONCLUSIONS

In any consideration of fever it is well to remember that normal body temperature is regulated by a central as well as a peripheral mechanism The heat regulating center probably resides in the hypothalamus The heat generated by the normal metabolic processes is eliminated through the lungs and skin in *such a way as to maintain the body temperature within a small* range A disturbance of the heat regulating or heat eliminating mechanism will cause a rise or fall in body temperature

The disposing factors to be taken into account include the environment the condition of the skin disease of the central nervous system and stimuli such as emotion that influence the hypothalamus as well as blood flow in the periphery

It is essential in assessing the significance of any elevation of body temperature above 98 6° to require the patient to keep a temperature chart and to record the time of menstruation in

women as well as other factors such as are mentioned above

There are many patients with a body temperature that fluctuates above and below 98 6° who have no signs of infection or any other disease Failure to understand this group of persons has led to a great many unnecessary examinations restriction of activity, and in some instances chronic invalidism

CHAPTER II

Diagnostic Procedures

In the diagnosis of prolonged and perplexing fever it is important to have a planned program of investigation in order to arrive at a definite decision as promptly as possible It is well to re call that the three commonest causes of prolonged fever are a specific infection a tumor or a blood dyscrasia (See Table 1 pages 7-8)

THE HISTORY

The history should cover the following points

1 Exposure to infections that commonly cause prolonged fever i e tuberculosis brucellosis tularemia malaria typhoid fever tonsillitis or sore throat

2 Previous infections especially acute rheumatic fever skin or re piratory infections uterine or intestinal infections and attacks of malaria Some infections of the internal organs including the lymph nodes kidneys muscles and bones are due to common pyogenic organisms and may cause illness several months or years after the initial infection No past infection however insignificant should be overlooked as a pos sible contributory factor

3 A history of tooth extraction or an operation about the mouth or jaws or a history of recent pregnancy These may be important in suggesting a source of infection A previous

operation may give a clue to the diagnosis of a recurrent tumor or an infection with fever

4 The use of drugs to which the patient may be hypersensitive

5 The presence of chills Rapid fluctuations in fever with chills may suggest diseases such as septic thrombophlebitis, endocarditis tuberculosis or malaria

6 Any previous episodes of fever The record of these may be helpful in the interpretation of relapsing types of fever

THE PHYSICAL EXAMINATION

In the physical examination special attention should be given to certain regions where positive information may aid greatly in diagnosis

The skin and mucous membranes should be examined for eruptions or petechial hemorrhages The presence of petechial hemorrhages especially in the conjunctival sac, the ocular fundi under the fingernails or in the lobes of the ear, suggests at once a bacterial endocarditis or one of the blood dyscrasias such as leukemia Erythematous eruptions over the face or extremities suggest acute lupus erythematosus and the eruption of enteric fever may be maculopapular

Clubbing of the fingers associated with fever suggests bacterial endocarditis a lung tumor or latent bronchiectasis When diarrhea is present clubbing of the fingers may suggest ulcerative colitis and with jaundice an infectious cirrhosis of the liver

Cardiac murmurs with fever should always suggest bacterial endocarditis or active rheumatic fever

Lymph node enlargement A search should be made for localized lymph node enlargement especially in the neck axillae, or groin Enlarged nodes may be due to tuberculosis

a metastatic tumor leukemia or lymphoma A node can usually be removed for histologic examination Lupus erythematosus disseminatus may cause fever and enlarged lymph nodes without a skin eruption

Splenomegaly Enlargement of the spleen with prolonged fever usually suggests an infection or a disorder of the lymphatic or hematopoietic system The associated features are extremely important For example splenomegaly with fever and a heart murmur suggests bacterial endocarditis Splenomegaly with fever and leukopenia suggests enteric fever brucellosis malaria or aleukemic leukemia or kala azar

An enlarged liver with fever should suggest a liver abscess or amebic hepatitis Also fatty infiltration or a tumor of the liver may be responsible for the enlargement and fever

The umbilicus should be examined for signs of a metastatic tumor or a fistula Intra abdominal tumors may metastasize to the umbilicus and fistulae may occur in chronic peritonitis due to tuberculosis or pneumococcal infection

The rectal and pelvic examination should be made in an attempt to detect signs of a tumor (rectal shelf) or an abscess

Retroperitoneal masses Masses in the flanks or the pelvis may arise in the retroperitoneum Those causing fever are tumors in kidney infections or lymphomas or sarcomas of the lymph nodes Finding such masses should lead one to examine the various organs involved

LABORATORY EXAMINATIONS

The laboratory examinations must be planned on the basis of the history and physical examination which may suggest certain diseases Laboratory examinations may be considered in two groups those which should be performed in all cases and those which should be performed only when indicated

The examinations mandatory in all cases include the following

1 Total blood count and smear, looking especially for anemia leukopenia or leukocytosis abnormal cells and sedimentation rate and malarial parasites
2 Urine examination for pyuria, bacteriuria, or hematuria
3 X ray examinations of chest
4 Blood culture aerobic and anaerobic
5 Examinations of stools for blood pus parasites and pathogenic organisms

From these examinations alone one is often able to make a diagnosis of many of the infections causing a prolonged fever If however they yield negative results other tests may be required They include the following

1 *Serologic tests* These are helpful in the diagnosis or exclusion of certain infectious diseases such as enteric fever brucellosis tularemia rickettsial diseases and syphilis

2 *Sputum examination* This should be carried out in all patients with cough and expectoration, and in all patients with changes shown by x ray examination

3 *Skin tests* The tuberculin test should be used in patients with prolonged fever without local signs and in cases where a lesion may be due to tuberculosis If the reaction is negative the evidence against tuberculosis is very good indeed Other skin reactions in the same category are the Frei test and the brucellin histoplasmin, and coccidioidin reaction

4 *X ray examination* X ray examination may be helpful in localizing the cause of a prolonged fever The chest should be x rayed to detect any lesions in the lungs mediastinum and ribs the clavicles or the upper ends of the humeri

When there is any question of a liver abscess with or without a subphrenic abscess a fluoroscopic examination should

be performed and films made in order to determine the level of the diaphragm and its movement A high diaphragm with restriction of movement may give the clue to the presence of a liver abscess When the diaphragm fails to move and is high the diagnosis of subphrenic abscess is suggested (See pages 74 and 83)

X ray examination of the bones for osteomyelitis or tumors is often diagnostic Secondary tumors of bone occur most often in the pelvis spine ribs the upper ends of the long bones and skull and in the case of osteomyelitis near the metaphysis so that these areas especially should be examined

Intravenous pyelograms are helpful in searching for a perirenal abscess a cortical abscess or a renal tumor Enlargement or displacement of the kidney and distortion of the pelvis are significant signs A perinephric abscess may be suggested from ordinary films when there i obliteration of the kidney shadow in the involved side with obliteration of the psoas shadow scoliosis of the lumbar spine with concavity toward the side of the lesion displacement of the colon and rarely a high diaphragm on the side of the abscess due to an extension into the subphrenic region

Gastrointestinal series are helpful in the diagnosis of tumors of the stomach or colon and enlargement of the liver or spleen They should be carried out in all cases of prolonged fever in which a lesion in this region is suspected

DIAGNOSTIC TESTS

The cause of fever can usually be determined with a minimum of laboratory examinations In cases of obscure fever however one is forced to depend on many tests to reach a definitive diagnosis If these tests are delayed an early cancer causing fever may become inoperable by the time it is dis

covered It should also be remembered that bacterial infections are most easily treated before there are far-distant metastatic foci

The blood should be examined to detect abnormal forms, including parasites (especially malaria) leukemia infectious mononucleosis and anemia Sternal marrow aspiration and biopsy are often of diagnostic value, not only for leukemia and multiple myeloma but occasionally for metastatic neoplastic ti sue cells Blood chemistry examinations include those for the total protein and albumin globulin ratio A high globulin is found in cirrhosis of the liver multiple myeloma lupus erythematosus Boeck s sarcoid periarteritis nodosa and some chronic infections An increased acid or alkaline phosphatase in the absence of jaundice may suggest a neoplasm Blood cultures are helpful in septicemias and bacteremias since the organisms are present early Undulant fever the typhoid fever group and gonococcal infections are often identified by this means Cultures should be grown under normal atmospheric conditions as well as under reduced oxygen tension Animal inoculation is worthwhile not only for isolating bacteria but also for identifying such conditions as Weil s disease Agglutination and complement fixation tests will help to diagnose typhoid fever paratyphoid fever dysentery undulant fever, tularemia rickettsial disease (Proteus) infectious mononucleosis (sheep cell) virus pneumonia (cold agglutinins) syphilis and gonorrhea

Urine examinations are also helpful in ruling out pyelonephritis and cystitis by cultural means Typhoid fever and septicemias also are often detected by this method Animal inoculation of the urine helps in the diagnosis of tuberculosis of the genitourinary tract as well as of Weil s disease An examination of the urinary sediment for evidence of pus red cells bacteria and crystals may help to limit the cause of fever to

the urinary tract Persistent or microscopic hematuria may be caused by tumor tuberculosis and silent urinary stone with pyelonephritis or bacterial endocarditis

Sputum obtained from the lungs or throat or by fasting gastric aspiration should be examined Cultures and animal inoculation identify tuberculosis, pyogenic organisms and mycoses Papanicolaou stains may identify tumor cells Microscopic examination should also be carried out for evidence of tuberculosis pneumococci streptococci staphylococci and fungus infections

Stool culture even without signs of localization of symptoms in the gastrointestinal tract should be carried out for the typhoid paratyphoid group as well as dysentery organisms Microscopic examination should be used to identify *Endamoeba histolytica* and red and white cells should be looked for as evidence of enteritis

Various other fluids which can be examined for evidence of hidden disease include spinal fluid pleural fluid (if present) ascitic fluid (if present) synovial fluid (if an excess amount can be demonstrated) prostatic fluid fluid from the female cervix and fluid from localized abscesses Cultures counts of various cells present as well as smears for bacteria and mycotic organisms should be carried out Chemical studies which should also be performed include those of total protein chlorides and sugar Serologic studies and colloidal gold determination should be made when the spinal fluid is obtained

Skin tests may be valuable diagnostic aids The tuberculin test is often helpful Other skin tests may help in detecting undulant fever tularemia trichinosis histoplasmosis and lymphopathia venereum (Frei test) The skin test for undulant fever should never be carried out until after the agglutinations have been repeated since the skin test may alter the titer greatly

X ray examinations which should be performed are as fol-

lows films of bones, sinuses, and teeth for evidence of in fection or neoplasms posteroanterior, lateral and oblique films of the chest for mediastinal, interlobar retrocardiac costophrenic and subdiaphragmatic pathology flat film of the abdomen for psoas outline for determining perinephric pa thology pyelography to rule out intrarenal or extrarenal pa thology and a complete study from the esophagus to the rectum for determining intrinsic and extrinsic pathology of the bowel

An electrocardiogram with study of the T waves and P R intervals helps to determine active rheumatic fever and peri carditis If nodes are found biop y should be carried out Un der certain circumstances surgical exploration is indicated Some of the conditions that cause prolonged fever that may be determined by this means are neoplasms tuberculosis Boeck s sarcoid lupus erythematosus periarteritis, trichinosis and cirrhosis of the liver

A test for excluding drug fever is the withdrawal of all medication Sulfonamides barbiturates and aminopyrine are the chief drugs to be suspected

PART TWO

Infectious Fevers

CHAPTER III

Tuberculosis

Of all the infections which may cause prolonged fever of ob scure origin tuberculosis is by far the commonest The lungs are the most frequent site of active tuberculous disease causing fever Attention is called to this region when the disease is punctuated by various episodes such as hemoptysis pleural effusion or an attack of pleurisy However not infrequently it is the constitu tional symptoms of an infection such as fever and loss of weight that cause the patient to seek advice In all patients with such symptoms a thorough physical and x ray examination of the chest should be made since early minimal lesions of tuberculosis may be found in this way and the diagnosis may be established In questionable cases the tuberculin test and gastric washings are valuable

When one decides that active pulmonary tuberculosis is not present to account for an obscure fever the possibility of tuber culosis elsewhere should be considered The most likely places for tuberculosis to focalize and give origin to prolonged and ob scure fever with few or no localizing signs are the lymph nodes (bronchial or abdominal) the pericardium and the bones

It must be remembered that in about 10 per cent of cases tuberculosis is found localized below the diaphragm which makes this disease difficult to establish by the usual x ray or phys ical examination For example Lewison *et al* (73) analyzed 893 autopsies where the cause of death was tuberculosis Of 148

cases diagnosed clinically as other than tuberculosis 95 proved to be pulmonary tuberculosis, 21 miliary tuberculosis 19 tuberculous meningitis 3 tuberculous peritonitis 2 tuberculous enteritis 3 bone and joint tuberculosis 3 Addison s disease caused by tuberculosis of the adrenal glands 1 lymph node tuberculosis, and 1 genitourinary tuberculosis

The general features suggesting tuberculous infection are the exposure of patients to tuberculosis previous evidence of active disease fever with a normal leukocyte count or leukopenia evidence of old or latent tuberculosis (lymph nodes lungs etc) positive tuberculin reactions, and the findings of possible tuberculosis by x ray examination of various organs

ILLUSTRATIVE CASES

The problems involved in the diagnosis of tuberculosis as the cause of prolonged fever are best presented through specific cases The following report abstracts are arranged according to the part of the body affected or the type of disease

FALLOPIAN TUBES

In the following case a patient with a history of chills and fever proved to have tuberculosis of the right tube and ovary Following operation the fever disappeared with recovery

CASE 1 A 24 year old woman complained of loss of weight for 6 months chills and high irregular fever for 2 months and increasing fatigability The chills usually lasted 30 minutes and occurred in the afternoon or evening associated with a temperature of 102 to 104 The family history was negative for tuberculosis

Physical examination revealed slight pallor of the skin and mucous membranes Pelvic examination disclosed a mass in

the right tubo ovarian region with tenderness on motion of the uterus

Laboratory data The urine was negative The red cell count was 3 800 000 the hemoglobin 70 per cent and the white cell count 11 400 Sputum examinations were negative for tuberculosis X ray examination of the chest showed increased peribronchial infiltration but no evidence of tuberculosis The blood sedimentation rate was 0 6 mm per minute An intracutaneous tuberculin test was strongly positive

Course Following admission the patient had chills at irregular intervals with a temperature rise to 100 to 104 Malaria blood smears blood cultures undulant fever agglutinations and stool cultures were negative The Widal test showed slight agglutination up to a dilution of 1 80 Other agglutinations (typhoid A and B heterophil and *Suis pestifer*) were negative Full mouth x rays gave no evidence of infection or tumor Sulfanilamide was given for 8 days with no effect on the chills and fever

An exploratory laparotomy performed 1 month after admission revealed a large inflammatory mass involving the right tubo ovarian region which contained pus A Meckel s diverticulum was adherent to another loop of ileum and apparently there was an internal fistula communicating between the two loops The diverticulum was excised the opening into the ileum was turned in and the appendix was removed The patient had a good convalescence and within 72 hours after operation the temperature returned to normal There was no recurrence of chills

The pathological report was tuberculous salpingo-oophoritis chronic appendicitis and periappendicitis and Meckel s diverticulum showing slight chronic inflammation

LIVER

In the following case chills and fever developed just before a full term delivery with liver enlargement and uterine bleeding Biopsy of the liver led to a diagnosis of endometrial and miliary tuberculosis There was a fatal termination

CASE 2 A 29 year-old Negress became pregnant 1 year after a pleurisy with effusion On the day before entry she had a shaking chill with fever to 102

At the age of 27 the patient had pneumonia and a year later she had pleurisy with effusion For 3 or 4 years before admission she had a chronic cough during the winter but repeated chest x rays were negative Two months prior to admission dull non radiating pain developed in the right upper quadrant lasting only 1 day Five days prior to admission pain in the lower abdomen and back started and lasted 6 days

Shortly after admission a normal full term male infant was delivered after a short labor About 24 hours after delivery the rectal temperature rose to 103

Laboratory data The urine had a specific gravity of 1 008 to 1 030 showed traces of albumin and sugar and was loaded with white cells on several occasions The sedimentation rate was 28 to 36 mm per hour the hematocrit 37 per cent and the hemoglobin 11 Gm per 100 cc The white cell count ranged from 5800 to 9150 The total protein was 6 Gm per 100 cc Cephalin flocculation was 1+ Nose and throat cultures yielded the normal flora and *Hemophilus influenzae* Two urine cultures contained *B pyocyaneus* and enterococci The Widal reaction was positive in a titer of 1 160 Brucella agglutinations were negative

Course The patient had a persistent temperature during her hospital stay with a peak of 102 5 during the first week On the thirteenth day she was started on 100 000 units of penicillin every 3 hours and 1 Gm of streptomycin daily By the sixteenth day the liver tenderness had greatly subsided At the end of the eighteenth day there was an increase in the rales at the right lung base The patient left the hospital against advice on the twenty first day

Ten days later she was readmitted with the chief complaint of profuse vaginal bleeding of 24 hours duration Fever had ranged between 100 and 102 A diagnosis of tuberculous endometritis was made by curettage and a biopsy of the liver at the time of surgical exploration for a possible subdiaphragmatic abscess showed miliary tuberculosis Chest x ray showed an accentuation of the bronchovascular markings at both lung bases with fine stippling and diminished excursion of the right diaphragm The patient was transferred to a sanatorium where she died

LYMPH NODES

In the following case a young woman with a low grade fever of 15 weeks duration developed abdominal pain and tenderness X ray examination revealed many calcified lymph nodes in the right lower quadrant The presumptive diagnosis was tuberculous lymph nodes

CASE 3 A 21 year-old woman complained of frequent infection of the upper respiratory tract slight cough and increasing fatigue of 1 year s duration

Four years before admission she had had scarlet fever Two years previously she had been admitted to another hospital because of dyspnea substernal pain and ankle edema of 3 weeks duration The diagnosis was acute rheumatic fever One year later a diagnosis of mitral stenosis due to rheumatic heart disease compensated was made

On physical examination the lungs revealed a rare rale in the right posterior axillary line On percussion the heart showed borderline enlargement to the left There was a soft systolic murmur at the apex No diastolic murmur was heard The blood pressure was 98/60 the temperature 98 6 the pulse 102 and the respirations 26

Laboratory data Urine specimens were negative The hemoglobin ranged between 85 and 97 per cent The red cell count ranged from 4 860 000 to 5 280 000 and the white cell count from 8000 to 14 000 with 57 to 77 per cent polymorphonuclear leukocytes Twelve blood cultures were negative Urine injected into a guinea pig was negative for tuberculosis The sedimentation rate ranged from 0 15 to 0 60 mm per minute An intradermal tuberculin test was highly positive in 1 1000 dilution X ray examination of the sinus revealed cloudy left frontal and ethmoid sinuses A chest plate taken on admission was interpreted as consistent with rheumatic heart disease (mitral stenosis) The electrocardiogram revealed no evidence of active rheumatic infection

Course The patient was placed on a 1200 calorie reducing diet Although there was no evidence of active heart disease or failure she had an intermittent elevation of temperature to 99 5 She was placed on salicylates for fleeting joint pains until the fourth week of hospitalization when she

developed mild symptoms of salicylism At the end of the fourth week she developed pain in the right lower quadrant of the abdomen and rectal examination showed some tenderness in the right vault At the beginning of the fifth week small erythematous papular skin lesions of the upper and lower extremities developed but lasted only a short time In the sixth week the temperature fluctuated to 100 5 and there developed definite hard papular skin lesions over both elbows During the next 4 weeks periodic fever occurred on the same day each week and lasted for about 2 days accompanied by headache increased malaise and pain in the back

During the twelfth week the periodic rhythm of the temperature stopped but the symptoms continued unabated In the fourteenth week a tuberculin skin test was positive in 1 1000 dilution A flat plate of the abdomen revealed calcified nodes in the right lower quadrant Two weeks later the patient was transferred to a tuberculosis sanatorium with a presumptive diagnosis of tuberculosis of abdominal lymph nodes

In the following case the excessive use of alcohol and barbiturates was followed by 18 weeks of high irregular fever A mass developed in the mid abdomen and death occurred following massive rectal bleeding The autopsy report was tabes mesenterica and acute rectal ulcer

CASE 4 A 39 year-old man complained of a chill on the day of entry

Nine months previously there was a clonic convulsion followed by unconsciousness Following this there were several episodes suggestive of petit mal The patient lost weight and developed a persistent cough with fever usually low grade but at times rising to 103 The cough was at times productive of whitish mucoid sputum The day before entry he had a severe chill lasting for 30 minutes after which the temperature rose to 105 with dyspnea and accentuation of the cough

On physical examination the temperature was 103 the pulse 90 the respirations 35 and the blood pressure 120/65 The patient was poorly developed and thin The lower abdomen was flat soft and nontender In the upper

mid abdomen there was considerable resistance and mild ten derness

Laboratory data The red cell count was 4 860 000 the hemoglobin 90 per cent and the hematocrit 42 per cent The white cell count ranged from 6600 to 14 400 The neutrophils averaged 80 per cent and there was a consistent increase in band forms *During the last 3 weeks of illness* there was leukopenia reaching a minimum of 2000 just prior to death The neutrophils still predominated On entry the blood urea nitrogen was 9 mg per 100 cc and the phenolsulfonphthalein excretion was 45 per cent in 2 hours (intramuscular method) Maximum specific gravity of the urine was 1 022 The total blood protein was 6 3 Gm per 100 cc with albumin 3 4 Gm and globulin 2 9 Gm The feces contained no blood The sputum on entry contained pneu mococcus type XI in large numbers but no tubercle bacilli A specimen 1 month after entry did not produce tuberculosis when injected into a guinea pig Guinea pig inoculation of the urine failed to reveal tuberculosis Three blood cultures were negative Agglutinations for typhoid paratyphoid and bru cellosis were negative

Course Four days after entry the patient had a general ized clonic convulsion followed by confusion and confabula tion which cleared in a few hours On the following day coarse bubbling rales were heard over the right lower lung *without any change in breath sounds On the twenty-eighth* day a hard nontender mass measuring about 10 by 10 cm was felt in the upper mid abdomen It moved only slightly with respirations and had a sharp lower margin The abdo men was generally distended with gas but was not tender The patient failed rapidly with progressive weight loss and severe anorexia The temperature ranged constantly between 101 and 104 Sulfadiazine failed to alter the fever or the downward course On the thirty first day chest x ray exami nation showed diffuse coarse mottling of both lungs with considerable Lipiodol residue in both lung bases On the fortieth day there was extensive diffus mottling throu hout both lungs The tuberculin test was repeated on the thirty ninth day and was negative *On the forty third day the* patient suddenly passed a quart of bright red blood by rec tum Emaciation fever prostration and anemia progressed steadily and the patient died on the fifty third day

The autopsy revealed massive conglomerate tuberculosis of

the mesenteric celiac and mediastinal lymph nodes There was also an acute ulcer of the rectum

In the following case a young woman developed an enlarged mediastinal lymph node after 3 weeks of high fever Biopsy showed this node to be tuberculous

CASE 5 A 25 year old Negress was admitted with loss of energy malaise fever and anorexia Ten days before admission her temperature was 102 and she developed a mild unproductive cough She continued to feel feverish with occasional chilly sensations and had a constantly elevated temperature between 101 and 103 The admission temperature was 102 6 the pulse rate 104 the respirations 25 and the blood pressure 110/70

Laboratory data Eight urine specimens were examined with the highest specific gravity 1 017 There was the slightest possible trace of albumin in one specimen 0 to 20 white cells in two and rare hyaline casts in one The hemoglobin was 64 5 to 70 2 per cent The red cell count was 3 800 000 to 4 200 000 and the white cell count 5600 to 3800 The stools were guaiac negative and cultures revealed no pathogenic organisms Blood agglutinations were negative for para typhoid A and B *B melitensis* and the dysentery group A tuberculin skin test was positive 1 10 000 The sedimentation rate was 0 10 mm per minute on admission and rose to 1 50 mm later in the course X ray examination of the chest showed an irregular density at the right lung root and slight widening of the supracardiac area from enlarged lymph nodes

Course The patient had a spiking temperature as high as 104 daily with lower daily readings between 99 and 101 On the eleventh hospital day an enlarged nontender lymph node was observed behind the right sternomastoid muscle and its attachment to the clavicle Biopsy of this node revealed tuberculosis and on the twenty fourth day the patient was transferred to a tuberculosis sanatorium

MILIARY TUBERCULOSIS

In the following case a middle aged woman with a history of rheumatic heart disease and symptoms of congestive heart failure had a 5 week episode of erythema nodosum without

fever followed by several months of relative well being She then had chilliness fever and painful swelling of the wrists and hands following a sore throat Fever persisted for 10 months until death Two months after the onset of fever the patient developed pulmonary infiltration with cavity formation The autopsy diagnosis was miliary tuberculosis

CASE 6 A 32 year-old woman complained of easy fatigability dyspnea and edema of the ankles of several years duration She had had rheumatic fever many years before and 2 months before admission noticed a crop of red tender nodules on the legs which lasted for 5 weeks She was discharged in 3 weeks with a diagnosis of rheumatic heart disease During this time she was afebrile Six weeks later she developed chilliness fever and pain and swelling of the wrists and hands She was admitted for the second time 1 week later with a temperature of 102

Physical examination revealed the throat to be injected. The heart was enlarged to the left There was a loud systolic murmur at the apex transmitted to the axilla P was accentuated The first sound at the apex was loud and snapping The blood pressure was 110/70 There was no swelling or tenderness of any joints

Laboratory data The urine and sputum were normal The white cell count was 15 600 A chest plate showed a mass to the right of the superior mediastinum and an enlarged heart with a mitral deformity The electrocardiogram showed a marked left ventricular preponderance Repeated blood cultures were negative except for one culture positive for *Streptococcus viridans* An agglutination test for undulant fever was negative

Course Two weeks after admission there was intermittent fever with temperature ranging from 97 to 104 which continued for almost 3 weeks There was a tender nonpulsating mass to the right of the manubrium and a brassy cough X ray examination showed an increase in the mediastinal mass and an interlobar density in the right mid-chest The course during x ray therapy was as follows

March 17 Interlobar density in right mid-chest
March 25 Small patch of density with hole in center

April 2 Wedge shaped density in right axillary border
April 9 Interlobar fluid
May 1 Infiltration in both upper lung fields
May 25 Small cavity in first interspace

Except for the development of small red tender nodules cultures from which yielded *Staphylococcus aureus* the course was uneventful until the eighth month when there was a sustained temperature of 102 to 104 for 2 weeks X ray and physical signs were consistent with pneumonia of the right lung base During the last few months of life the patient developed enlarged swollen tender knees Death occurred suddenly 10 months after the onset of fever

The clinical diagnosis was mediastinal abscess rheumatic heart disease pneumonitis pleuritis and septic arthritis The gross anatomical diagnosis was old pleurisy with abscess formation retropleural abscess purulent arthritis cardiac hypertrophy chronic passive congestion of the liver and enlargement of the kidneys The microscopic diagnosis was tuberculosis of the lung pleura spleen and rib Microscopic study of autopsy material showed miliary tuberculosis

In the following case a young woman had fever for several weeks followed by severe frontal headaches and double vision She then developed miliary tuberculosis and meningitis which caused death 3½ months after the onset of illness

CASE 7 A 23 year-old housewife was admitted complaining of double vision and constant sharp frontal headaches of 2 weeks duration

Three months before admission the patient had developed anorexia and sharp constricting pain in the back with girdle distribution One month later she observed increased warmth and noticeable perspiration She went to an outpatient clinic where spinal x rays were negative and fever was determined for the first time Blood agglutination for typhoid was elevated and she was admitted to the hospital During 27 days of hospitalization the white cell count ranged from 3000 to 6000 Five stool cultures were negative for pathogens The patient had a swinging temperature with rises to 103 for the first 2 weeks after which the temperature dropped to 99 She improved and was discharged on the twenty seventh day with a diagnosis of fever of unknown etiology The spleen was palpable at this time

Shortly after returning home the patient developed a chronic nonproductive cough which lasted for 2 weeks She continued to feel weak and her afternoon temperature returned the highest recorded being 102 3 weeks prior to the next hospitalization Two weeks before entry she had severe frontal headache There had also been double vision One week before entry there were several episodes of nausea and vomiting with an increase in anorexia

Physical examination revealed several small furuncles on the forehead Extraocular movements were intact except for deviation of the right eye laterally beyond the midline when looking straight ahead The right eardrum was slightly in jected in the posterior portion There was no gross impair ment of hearing There was moderate rigidity of the neck There was a suggestive Kernig s sign bilaterally Other re flexes were physiologic

Laboratory data A blood Hinton test was negative There was a trace of albumin on one occasion but no sugar The sediment revealed 5 to 10 white cells per high power field The red cell count ranged from 4 700 000 to 5 300 000 and the hemoglobin from 12 to 14 Gm On admission the white cell count was 6400 with 64 per cent polymorphonuclear leukocytes 21 per cent lymphocytes 10 per cent monocytes 3 per cent eosinophils and 2 per cent basophils There was a gradual increase in white cells to 14 700 with a predomi nance of polymorphonuclear leukocytes The nonprotein ni trogen ranged from 34 to 37 mg per 100 cc The fasting blood sugar was 104 mg per 100 cc the total protein 4 94 mg per 100 cc albumin 4 6 Gm and globulin 1 94 Gm The blood culture showed *Staph aureus* and diphtheroids A tu berculin skin test showed a 3 mm induration with no ery thema A lumbar puncture on the second hospital day showed an initial pressure of 20 mm of water the color was clear the total protein was 90 mg per 100 cc and chlorides 675 mg the colloidal gold was 1122332100 serologic reactions were negative a routine culture showed no growth there were 50 lymphocytes per cubic centimeter the final pressure was 100 mm Repeated lumbar punctures showed a gradual rise in the initial pressure to 400 mm The total protein increased to 210 mg Chlorides decreased to a low of 576 mg per cent The sugar likewise decreased to a low of 20 mg After ten guinea pigs had been inoculated another lumbar puncture specimen showed pellicle forma

tion which on smearing revealed two clumps of acid fast organisms Late in the course of the illness a chest plate indicated increased lung infiltration

Course Throughout her hospital stay the patient appeared acutely ill and complained bitterly of headache and weakness She vomited intermittently Perspiration was marked The temperature ranged between 100 and 103 Repeated examination of the fundi after dilation of the pupils failed to reveal tubercles The chest remained clear On the tenth hospital day the patient became irrational and hallucinated Stiffness of the neck increased greatly and the pulse became very rapid No friction rub was heard After this the patient became semistuporous and breathing became stertorous There was then blurring of the optic disk margins The patient expired on the sixteenth hospital day 3½ months after the onset of her illness Death was due to miliary tuberculosis and meningitis

PERICARDITIS

In the following case an elderly man had persistent high fever for more than 6 weeks accompanied by weakness loss of weight and dyspnea thoracic pain on exertion and a transitory pericardial friction rub There was progressive heart failure over a period of 12 weeks when death occurred The post mortem examination revealed tuberculous pericarditis

CASE 8 A 70 year old Negro was admitted complaining of shortness of breath and weakness For 2 years he had felt a constriction across the chest and upper abdomen without exertion Two months before admission progressive weakness began and continued for 6 weeks accompanied by dyspnea loss of weight and sleeplessness

Physical examination showed moderate dyspnea at bed rest and evidence of arteriosclerosis There was localized tenderness over the left pectoralis major muscle On percussion the heart was found to be enlarged to the left The impulses were feeble and the sounds were distant The blood pressure was 144/66

Laboratory data The red cell count was 4 800 000 and

the white cell count 5900 The hemoglobin was 90 per cent Urine and blood cultures were negative A chest plate and electrocardiogram were within normal limits

Course The patient continued to lose weight and strength Temperature ranged between 100 and 103 After several weeks a friction rub was heard over the heart for 2 days Thereafter there was increase in the area of cardiac dullness The heart sounds became more distant and signs of cardiac failure developed The patient had attacks of tachy cardia and during the terminal attack he collapsed and died The duration of his illness was 12 weeks and fever was present for more than 6 weeks Post mortem examination re vealed tuberculous pericarditis

CHAPTER IV

Local Septic Infections Common Regions and Causes

BACTERIAL ENDOCARDITIS

Of the local septic infections causing prolonged fever, bacterial endocarditis is the commonest There are rare cases of sepsis in which the patient dies before the vegetations on the valves have caused ulceration or in which they are localized on the aortic wall (endaortitis) without endocarditis The latter localization is seen occasionally in coarctation of the aorta In many instances acute endocarditis is only an incidental finding during the course of a septic infection and may give rise to no localizing cardiac signs The presence of a streptococcal infection on the valves of the left side of the heart may be suspected when the blood cultures are persistently positive and there are signs of embolic phenomena in the peripheral circulation with localizing cardiac signs found on physical examination

When there are signs of sepsis without positive blood cultures and without localized signs of infection the tricuspid or pulmonic valve may be suspected In these cases embolic phenomena in the lesser circulation such as pulmonary infarctions or metastatic bronchopneumonia, may aid in the diagnosis of bacterial endocarditis However without the presence of a valvular murmur the diagnosis may not be possible inasmuch as the primary focus for the septic infection may be

in the pelvic or other veins and give rise to pulmonary metasta ses without endocarditis Often pelvic and other veins contain infection which is not detectable When a known primary focus heals as occurs in some cases of pelvic or tonsillar infec tion and the metastatic lesions progress endocarditis should be suspected especially if there are embolic phenomena in the greater or lesser circulation and blood cultures are persistently positive

Other cases of bacterial endocarditis causing fever of obscure origin are those without bacteremia This situation is sometimes encountered when the vegetations are located on the valves of the right side of the heart or when the lesions are fibrosing so that only a very few organisms get into the circulating blood The latter condition is occasionally encountered in patients with fever which has persisted despite the giving of large amounts of penicillin

In summary it may be said that whenever a patient has a persistent low grade fever and constitutional symptoms of an infection with the signs of valvular heart disease with or with out congestive heart failure progressive renal failure anemia with splenomegaly or embolic phenomena a bacterial endocar ditis must be strongly suspected

The cases in which the diagnosis may be difficult are those in which the disease is active but no signs of valvular disease are present tho e in which there are no cardiac murmurs or bacteremia and those in which embolic phenomena or an en larged spleen and anemia are the outstanding features Since there are satisfactory methods for treating bacterial endocardi tis every attempt should be made to recognize this infection early

Cases with No Signs of Valvular Disease Rarely one encounters cases of bacterial endocarditis in which there are no

signs of valvular disease at any time during the course of the disease In most cases, however, these signs appear if the patient survives 6 weeks or longer The cases without heart murmurs are almost invariably those of infection of previously normal heart valves especially when the endocarditis is acute and the infection is of relatively short duration so that the heart valves do not become insufficient through destruction As a general rule the endocarditis in these cases is only a part of a more widespread infection with many metastases or it occurs as a complication of some chronic disease, such as cirrhosis of the liver ulcerating tumors of various organs or leukemia

Endocarditis should be suspected in the absence of signs of valvular heart disease if there is bacteremia without an obvious focus of infection or emboli to various organs If a cardiac murmur appears the diagnosis is more certain We have seen several ca es of bacterial endocarditis in which the vegetations were situated on the aortic valves below the line of closure and grew downward toward the mitral valve without ulceration At autopsy the vegetations were located on previously normal valves and there were no signs of destruction Very often there were signs of infection for 6 to 8 weeks or longer The infecting organism may be the gonococcus or pneumococcus

Cases without Cardiac Murmurs or Bacteremia These cases are exceedingly rare and the diagnosis is usually made by the pathologist However since they suggest certain points that are important in pathogenesis they should be mentioned here The cases that we have observed have been similar to those described above except that there was no bacteremia Of considerable significance are the cases in which there is an infective aortitis with mycotic aneurysm formation (infective endaortitis) and no valvular murmurs occur until the aneurysm becomes large enough to cause deformity of the orifice of the aortic valve

In such cases the blood cultures may be negative for several months Crane (*74*) has recently reported such a case and Aschner (*75*) has recorded similar experiences with gonococcal infection

Streptococcal Endocarditis The following cases are presented to show the difficulties encountered in patients with streptococcal endocarditis

In the following case fever and chills persisted for 9 months despite treatment There was progressive enlargement of the liver and spleen but no bacteremia The autopsy showed bacterial endocarditis from *Str viridans*

CASE 1 A 58 year-old man was admitted complaining of fever of 9 months duration Eight months previously he had entered a hospital in another city because of back pain associated with urinary symptoms of 1 month s duration The urine contained many white cells the prostate was enlarged and boggy the prostatic secretions contained many cells and sulfathiazole was given

One week later extreme tenderness was noted in the right costovertebral angle and pain began in the right flank radiating to the right lower quadrant of the abdomen Physical examination showed the heart to be slightly enlarged to the left The sinus rhythm was normal There was a mitral systolic murmur with accentuation of the first mitral sound Abdominal examination revealed a questionable enlarged liver The spleen was not palpable

On the third hospital day an afternoon chill occurred followed by a temperature of 104 2 Blood cultures were negative Pyelograms revealed a hydronephrosis of the left upper calyx and the urine culture yielded *Escherichia coli* The patient was given 0 5 Gm of streptomycin every 6 hours and the temperature returned to normal

The patient was readmitted a month later with the chief complaint of weakness and fatigue He had had a daily temperature elevation between 100 and 102 Two weeks previously he had had several morning chills He was placed on quinine and the chills disappeared but the regular afternoon fever persisted He was again given streptomycin Urine cul

tures grew out hemolytic *Staph albus* Malarial smears of the blood failed to reveal parasites

On the ninth day a transurethral prostatectomy was performed Because of the presence of hemolytic *Staph albus* the patient was given penicillin with an encouraging response On the thirty first day the liver was palpated Eleven days later axillary and inguinal lymph nodes were noted and due to the fact that fever had recurred the penicillin dosage was increased to 4 800 000 units daily and was given for 21 days

Three weeks later the patient again had acute pain in the left flank The urine revealed no stones crystals or blood cells Penicillin was discontinued 2 weeks later and 6 days afterward the fever recurred Penicillin was again instituted and the temperature came down to normal in 5 days Two weeks later penicillin was again discontinued and 2 days later fever recurred The white cell count ranged from 7000 to 10 000

Five weeks after the recurrence of fever an exploratory laparotomy was performed The liver was enlarged brownish purple red and firm with no adhesions The spleen appeared to be enlarged On palpation the kidneys were found to be normal sized

One week later the patient had acute severe pain in both shoulders Fever recurred 1 week later accompanied by aching in the legs and tenderness in the right knee Because of this aspirin was given with some response in temperature and symptomatology

Physical examination at this time revealed a few hemangiomas over the right abdomen and slight ptosis of the left eyelid The fundi showed early arteriosclerotic changes but no hemorrhages or exudates The lungs were clear on percussion and auscultation The blood pressure was 130/60 There was a loud systolic murmur over the precordium loudest at the apex No diastolic murmur was heard P_2 was equal to A The heart was enlarged 12 cm to the left of the mid sternal line in the fifth intercostal space The liver was enlarged 5 cm below the right costal margin and was slightly tender The abdomen heaved with aortic pulsations

Laboratory data A blood Hinton test was negative The urine pH was 6 5 the color was amber the specific gravity was 1 012 to 1 004 The slightest perceptible trace of albumin was present The urine sediment revealed 2 to 3

white cells per high power field No sugar ketones or bile were noted The urine culture revealed a rare *E coli* and a rare enterococcus Bence Jones protein was negative The sedimentation rate was 28 to 30 mm per hour The hemoglobin was 12 0 Gm and the hematocrit 35 per cent The mean corpuscular hemoglobin concentration was 33 to 34 3 per cent The white cell count was 8650 with a normal differential The icterus index was 7 The nonprotein nitrogen was 33 mg per 100 cc The total protein was 5 85 Gm per 100 cc with an albumin globulin ratio of 1 08 1 Blood cultures were negative

X ray examination of the chest revealed no evidence of active pulmonary disease There was thickening of the apical pleura on both sides with multiple foci of calcification in the left apex and infraclavicular region There was no evidence of bone disease Sternal marrow aspiration showed an increase in the number of plasma cells and the possibility of multiple myeloma was entertained

Course The daily temperature ranged for the most part up to 100 4 except on the eighth hospital day when it reached 101 6 The pulse paralleled the temperature and was never above 100 The chief complaint was occasional pain in the left shoulder The diagnosis at autopsy was subacute bacterial endocarditis from *Str viridans*

In the following case fever purpura progressive enlargement of the liver and spleen with leukopenia and thrombopenia and a systolic mitral murmur were the outstanding features There was no bacteremia

CASE 2 A 49 year old woman complained of purpura of 1 month s duration and fatigue and weakness of 3 months duration Twelve years previously excessive vaginal bleeding had been relieved by dilation and curettage followed by x ray therapy to the ovaries For 7 years she had injections for varicose veins the last time 1 week before admission Ten years before admission she had all her teeth removed with no excessive bleeding During the 5 months before admission there had been a progressive weight loss from 157 to 125 pounds

Three months before admission there was onset of constant pain in the epigastrium which occasionally radiated through to the back up to the left shoulder and down the

middle of the back in the lumbar region Pain was not re lated to change of position or food intake At the onset of the pain the patient had period of feeling cold and then warm to ether with night sweats She also had a cough pro ductive of white phlegm occasionally blood streaked There was progressive anorexia and fatigue One month before ad mission a nasal polyp was removed with bleeding for 3 days thereafter Two weeks prior to admission red spots appeared on the skin of the arms and legs and increased in number Beginning about this time there was morning nausea and vomiting One week before admission bloody sores appeared at the corner of the mouth

On admission the temperature was 100 2 the pulse 90 the respirations 20 and the blood pressure 108/62 The skin showed numerous petechial hemorrhages on the arms and legs most marked over the lower right leg where there were some purpuric lesions There were also petechiae over the trunk and face over the palate and in the vagina The lungs were clear The heart was not enlarged A grade 2 systolic murmur was heard in the second right intercostal space The liver edge was felt 4 cm below the right costal margin The spleen was palpable 3 cm below the left costal margin

Laboratory data A blood Hinton test was negative The urine showed 1+ albumin no sugar ketones or bile and a few red cells The blood sedimentation rate was 80 mm per hour The red cell count was 3 200 000 the hematocrit 31 per cent and the hemoglobin 9 4 Gm per 100 cc The mean corpuscular volume was 97 and the mean corpuscular hemoglobin concentration 30 4 per cent Reticulocytes ranged from 3 1 to 1 5 per cent The white cell count ranged from 6850 to 3700 with 56 to 62 per cent polymorphonuclear leukocytes 32 to 37 per cent lymphocytes and occasional plasma cells and atypical lymphocytes The nonprotein nitro gen was 45 to 64 mg per 100 cc The total protein ranged from 6 96 to 7 80 Gm per 10 cc A blood culture was negative The alkaline phosphatase was 10 54 mg per 100 cc

X ray examination of the skull showed a diffuse hyperos tosis of the frontal bone The lung fields were clear There was symmetrical enlargement of the heart There were small suspicious osteolytic lesions in the left fifth and sixth po te rior ribs Bone marrow aspiration revealed large numbers of

plasma cells and plasmablasts and the erythrocytic series was considered to be hyperplastic

Course The patient had an almost daily temperature ris ing to between 100 and 101 Following x ray therapy the temperature rose as high as 103 4 The patient had repeated episodes of epistaxis During her stay she received 3 units of whole blood and 2 units of red cells Starting on the thirty eighth hospital day a course of six x ray treatments varying from 50 to 200 r was given The patient was discharged symptomatically improved on the tenth hospital day

Three months after discharge the patient was readmitted She had continued to have sharp pain in the epigastrium lasting about 1 hour and then disappearing only to return in about a day The abdomen was enlarged and 4 days before readmission a physician had withdrawn 8 quarts of fluid by abdominal paracentesis

Physical examination showed the sclerae to be slightly icteric There were a few scattered rales on deep inspiration The heart was enlarged being 10 5 cm from the mid sternal line There was a grade 2 systolic murmur over the entire precordium The abdomen showed shifting dullness in the flanks The liver edge was palpable and the spleen extended 5 cm below the costal margin

Laboratory data The urine had a specific gravity ranging up to 1 020 the albumin was 1+ bile was present on two occasions The blood sedimentation rate was 90 mm per hour The hematocrit was 26 to 31 per cent The hemoglobin was 8 4 to 10 9 Gm per 100 cc The white cell count ranged from 2750 to 5200 and was 2800 at the time of discharge Polymorphonuclear leukocytes varied from 69 to 92 per cent Alkaline phosphatase was 8 88 Bodansky units The ascitic fluid on two occasions was yellow and hazy and contained from 18 to 168 cells 80 per cent red cells and the rest lymphocytes Culture revealed no growth The bleed ing time was 2 minutes 15 seconds and the clotting time 2 minutes 45 seconds

Course The average daily temperature was 99 4 ex cept for several isolated elevations as high as 101 6 The patient was given 6 millicuries of radioactive phosphorus and crude liver extract intramuscularly There was daily dull upper abdominal pain which occasionally became severe enough to require Dilaudid The patient was discharged im proved on the forty fourth hospital day

About 2 months after discharge the patient developed multiple petechial hemorrhages which became confluent Large purpuric spots appeared in scattered areas over the torso She was given supportive therapy but failed steadily Six weeks later she had a massive hematemesis and died

Post mortem examination showed subacute bacterial endocarditis with no evidence of multiple myeloma

In the following case there were negative blood cultures chills and fever, purpura progressive anemia faint systolic murmur and cardiac insufficiency Autopsy showed bacterial endocarditis due to an unidentified Gram negative bacillus

CASE 3 A 51 year old man complained for 5 weeks of vomiting after eating without nausea or pain Eight weeks before entry his stools were black This symptom persisted for 3 weeks

Three and one half weeks before entry the patient was awakened three times in one night by drenching sweats The following afternoon he noted numerous blisters 1 to 2 cm in diameter on the extensor surface of the extremities These were described as reddish vesicular and itching The lesions subsided in 24 hours and did not reappear One week be fore admission he had a shaking chill which lasted for 10 minutes Nocturia once nightly appeared at the onset of the illness There was a weight loss of 20 pounds in the 4 weeks before admission The patient had consumed large amounts of alcohol for at least 5 years

Physical examination revealed pinhead sized reddish papu lar eruptions on the skin of the shoulder back and elbows There were pinpoint sized red hemorrhagic spots in the con junctivae of the lower lids Both jaws were edentulous The tongue was coated The liver was enlarged 7 cm below the right costal margin in the mid clavicular line The edge was smooth and slightly tender The spleen was not palpable The deep tendon reflexes were hyperactive The blood pres sure was 110/50 the temperature 103 , the pulse 100 and the respirations 24

Laboratory data The urine and stools were negative The hemoglobin was 40 per cent the red cell count 2 130 000 and the white cell count 12 450 with 59 per cent poly morphonuclear leukocytes On admission the nonprotein ni

trogen was 30 mg per 100 cc and rose in 1 month to 171 mg The total protein fell from 5 1 to 4 25 mg per 100 cc The carbon dioxide combining power fell to 15 vol per cent Twelve blood cultures two of them from an artery were negative For 2 days before death three blood cultures were positive for *Staph aureus* Agglutinations of the blood serum were negative for the enteric group *B melitensis* and *B tularensis*

A Brom ulphalein test for liver function showed all the dye removed at the end of 30 minutes There was a 4+ guaiac reaction to all specimens of gastric juice and mi croscopic examination revealed 15 to 20 red cells An elec trocardiogram revealed a prolonged Q T interval which was interpreted as consistent with myocardial disease A gastro intestinal series revealed a duodenal ulcer

Course The patient had a daily spiking temperature of between 102 and 105 There were several shaking chills in the afternoon shooting pains in the calves of the legs and severe testicular pain Epigastric pain appeared on the tenth day 2 hours after a meal and persisted for 2 hours Small hemorrhagic spots appeared in the conjunctivae and buccal mucosa

On the second day a soft systolic murmur was heard which did not appear to change during the course The liver did not change in size At the beginning of the third week edema of the lower extremities was noted and progressed

On the fifteenth hospital day 600 cc of citrated whole blood was given from a polycythemic patient Albuminuria and microscopic hematuria were noted thereafter for the first time Following the transfusion there was tachycardia hy perpnea and intense suffusion of the skin of the entire body with blood with a temperature rise to only 99 The patient passed no urine for the 12 hours following transfusion Urine concentration which had been as high as 1 018 was never above 1 012 thereafter The serum protein then dropped finally with a reversal of the albumin globulin ratio

During the week following the transfusion there was com plete remission of fever with a drop of pulse rate from 120 to 90 At the end of this week there was progressive daily spiking fever until it reached 102 During the fourth week the patient lapsed into a stuporous condition with in continence of urine and feces He was given another trans

fusion without benefit Mild icterus appeared late in the course Coarse rales appeared in the lower lung fields and the patient expired on the thirty third hospital day

ABSCESSES OF THE LIVER AND SUBPHRENIC SPACE

Liver abscesses causing obscure fever are either single or multiple Single abscess of the liver is almost invariably due to *E histolytica* Rarely it is due to a pyogenic infection and from such abscesses gonococci staphylococci *B melitensis*, pneumococci Friedlander s bacilli typhoid bacilli Salmonella organisms and Streptothrix may be isolated There are also rare instances of single abscess of the liver described in *E coli* infections following acute appendicitis acute diverticulitis or acute cholecystitis Fever from these may occur when the original focus is latent or has ceased to cause symptoms Occasionally an impaction of a stone in the hepatic duct may lead to multiple liver abscesses Liver abscess is usually secondary to a focus of infection in the portal venous system or to cholangitis More rarely it arises from an extension of infection in a neighboring organ or from a hematogenous metastasis

The commonest causes of infection in the portal area producing abscess are amebiasis and appendicitis Abscesses that develop through infections of biliary passages are due to stones in the common duct with cholangitis and cancer of the gall bladder Abscesses that arise from direct extension are seen most often in empyema and in infections of the gallbladder Metastatic abscess is due most often to a staphylococcal sepsis or otitis media

The diagnosis of liver abscess as a cause of prolonged fever is usually based on one or more of the following points

1 The recognition of a possible source of infection
2 The signs of a septic infection — fever chills sweats malaise loss of energy and weight and leukocytosis
3 Localized signs of liver disease such as hepatic enlargement, deep seated *pain in the hypochondrium elevations* of the diaphragm and friction rub over the liver and uterus
4 Presence of a complication of a sort that arises from a liver abscess

Sources of Infection An abscess of the liver develops most often from a focus of infection in the organs drained by the *radicles of the portal vein or by direct extension of infection* into the liver substance from a neighboring organ or through the biliary passages Less often the abscess is metastatic from areas outside the abdominal cavity It is well to remember that in 25 to 50 per cent of cases the source of infection is not obvious

X ray examination of the diaphragm in patients with suspected liver abscess is most important The first point to be noted is elevation and restriction of the movement of the diaphragm which may provide an important clue In some cases however a liver abscess may produce no change in the normal appearance of the liver by x ray

When a subphrenic abscess complicates a liver abscess there is obliteration of the costophrenic angle in the anterior and lateral view In subphrenic abscess due to other causes there is obliteration of the costophrenic angle in the anteroposterior view or *of the posterior costophrenic angle in the lateral view*

Air is present in a subphrenic abscess in only about 20 per cent of cases Its presence is diagnostic but its absence is not

Occasionally a liver abscess may be suspected from one of its

complications such as subphrenic abscess empyema lung ab scess hydrothorax, or peritonitis

Amebic Hepatitis On rare occasions in patients who have had an amebic dysentery which has become latent low grade irregular fever is present Diarrhea may not be striking or may be absent In such patients the presence of fever with slight en largement of the liver and pain over the lower right costal margin may suggest amebic hepatitis without abscess formation In deed in any patient a gradually enlarging liver with fever with or without leukocytosis should suggest the presence of amebic infection of the liver The finding of cysts or active amebae in the stools together with the disappearance of the fever hepatic enlargement and right sided pain following specific treatment with emetine usually settles the diagnosis

Habein (*76*) reported an interesting case of obscure fever which was finally diagnosed as amebic hepatitis after an illness of 17 months characterized by recurrent fever and loss of weight and strength The patient had had an attack of amebic dysentery 18 months before he was finally relieved of his hepatitis by means of chemotherapy

Multiple Abscesses Following Appendicitis and Pylephlebitis The following case is an example of appendicitis with metastatic liver abscesses and prolonged fever

Case 4 A 30 year-old man was ill for 7 weeks with fever The onset was abrupt with a chilly sensation malaise nausea and vomiting cramps abdominal pain and constipa tion Pain was severe One week after onset the temperature reached 104 A cough developed a tentative diagnosis of pneumonia was made and sulfanilamide was started There was no improvement over a period of 4 weeks when the pa tient became delirious and jaundiced and was admitted to the hospital

Physical examination showed jaundice flame shaped hem

orrhages in the retina moderate enlargement of the liver and spleen fever and tachycardia and slight abdominal distention

Laboratory tests showed bile in the urine and anemia The red cell count was 3 000 000 the hemoglobin 55 per cent and the white cell count 32 000 to 54 000 The icterus index was 55

Course There was progressive failure with chills fever increasing anemia persistent jaundice abdominal distention ascites hematuria and signs of bronchopneumonia Death occurred in the seventh week of illness The autopsy showed acute appendicitis with thrombophlebitis of the appendiceal veins enlargement of the liver and multiple abscesses splenomegaly and ascites

Chronic Cholangitis with Multiple Liver Abscesses The following case is representative of chronic cholangitis with multiple liver abscesses interpreted for a time as an obscure fever

CASE 5 A 39 year old woman complained of pain in the right shoulder of 4 days duration Two months before entry she began to have repeated attacks of mid epigastric pain and chilly sensations Two weeks before admission the number of attacks decreased Three days before admission she began to have a steady dull ache across the right shoulder and over the right side of the lower part of the neck In the 12 hours before admission she had onset of a dull ache below the mid right costal margin About the same time there was severe colicky pain in the right upper quadrant of the abdomen The patient had previously belched large amounts of gas but had had no vomiting At the time of entry she had a slight unproductive cough In the week before admission she had nocturia

Physical examination showed the tongue to be heavily coated The skin was hot and moist There was moderate tenderness in the right upper quadrant below the midpoint of the right costal margin

Laboratory data The urine specimens showed a trace of albumin with bile in about half of twenty specimens tested The sediment revealed 0 to 100 white cells occasional red cells and no casts The hemoglobin was 12 0 Gm per 100 milliliters The white cell count was 15 200 on admission rose

to 44 000 during the second week and then gradually fell to between 15 000 and 20 000 The polymorphonuclear leukocyte percentage averaged 75 Three blood Hinton tests were positive The icteric index was 5 on admission rose to 50 during the second week and then gradually fell to less than 5 thereafter The Ivy bleeding time was 2 5 minutes The total protein was 6 8 Gm per 100 cc The albumin was 3 2 Gm and the globulin 3 6 Gm The serum cholesterol was 82 mg The urobilinogen was 1 64 on entry rose to 1 256 during the second week and then fell to 1 32 A blood culture was negative The urine culture yielded *Staph aureus*

A chest film taken on the second hospital day revealed a pneumonic process at the right lung base At the end of the first week the interpretation was pneumonic process at the left lung base The tenth day film revealed a homogeneous density at the top of the right diaphragm consistent with encapsulated fluid At the end of the second week the right diaphragm was markedly elevated consistent with subphrenic disease Fluoroscopic examination revealed that the diaphragm moved with respiration and that the lung was clear above An intravenous Graham test revealed no filling of the gallbladder A pyelogram revealed only an enlarged spleen No opaque calculi were seen There was moderate dilatation of the right kidney pelvis and ureter

Course During the first 2 weeks the temperature ranged between 98 and 102 and the pulse between 95 and 140 During the second 2 weeks the temperature was 98 to 100 with the pulse between 90 and 110 During the fifth and sixth weeks the temperature ranged between 98 and 101 with the pulse between 90 and 110 In the seventh week there was a spiking temperature of between 98 and 102 with the pulse rising to between 100 and 120 Thereafter the temperature fell terminally to 100 with the pulse between 90 and 125

Treatment consisted of force fluids and a low fat high carbohydrate diet On the day after admission a few rales were heard at the left lung base and the following day there were definite signs of pneumonia at the right lung base Thereafter rales were continually heard at the right lung base posteriorly The right diaphragm was elevated during most of the course At the end of the second week a tap was performed at the right lung base but no fluid was obtained During the first 2 weeks the patient had considerable epigastric pain

Tenderness in the right upper quadrant disappeared after the third week In the sixth week another chest tap was attempted and the needle was felt to pass through a thick wall which was either pleura or diaphragm

In the eighth week the patient died Autopsy revealed chronic cholangitis with multiple liver abscesses

Stone in the Common Duct or Hepatic Duct Attacks of pain in the right upper quadrant jaundice with fever or intolerance to fatty foods with evidence by x ray of a nonfunctional gallbladder generally lead to a diagnosis of stones in the gall bladder or biliary tract In a review of 219 consecutive cases in which stones were present in the common duct Trueman (77) found that approximately 35 per cent of the patients were never jaundiced and 63 per cent had never had chills or fever

Walters and Snell (78) reported an interesting case of a 49 year old man who had had intermittent fever for many months with no jaundice or painful symptoms simulating disease of the gallbladder A cholecystogram had shown a normally functioning gallbladder At operation although the gall bladder was somewhat thickened stones were not found to be present within its lumen The common and hepatic ducts however were greatly dilated and contained several stones 1 5 cm in diameter

This case serves as an example of prolonged fever associated with stones in the common bile duct without jaundice and with no attacks of biliary colic It is well to consider this possibility in patients with recurrent chills and fever and to concentrate attention on the biliary tract Duodenal drainage and a search for cholesterol or bilirubin crystals may aid in the preoperative diagnosis

Acute Massive Necrosis Another form of hepatitis of non bacterial origin that may cause fever and be confused with multi-

ple liver abscesses is acute massive necrosis The following case is an example

CASE 6 A 36 year-old man complained of weakness fatigue and fever of 1 month s duration

Frequent attacks of tonsillitis occurred in childhood without any joint pains A year and a half before admission the patient received a laceration of the right eye and fracture of the frontal bone in an automobile accident without unconsciousness For 2 years he had had a chronic nonproductive cough with a slight amount of blood streaked sputum on several occasions the last one being 6 months before admission Bleeding hemorrhoids had been present for the past 6 months For 1½ years the patient had become lazy and shiftless and had drunk to excess

Seven months prior to admission there was onset of fatigue and anorexia Six months later there was marked increase in these symptoms together with an increase in body temperature Twenty five days before admission the patient s physician noted a temperature of 102 pharyngeal injection and ulceration The spleen was definitely palpable and the liver was enlarged but the edge was not definitely identified The white cell count was 1800 with 50 per cent polymorphonuclear leukocytes The hemoglobin was 72 per cent Twenty days before admission the patient entered a local hospital where he was given Pentnucleotide and sulfadiazine which was discontinued 3 days later due to albuminuria and red cells in the urine The temperature ranged between 101 and 105 with daily spikes A flat plate of the abdomen showed splenomegaly and displacement of the left kidney A sternal puncture was negative for agranulocytosis or abnormal cells. A 10-pound weight loss occurred in 4 months

At physical examination the patient was somewhat dehydrated and acutely ill with an increased respiratory rate and a slight cyanotic tinge to the lips The exposed areas of the skin were bronze with a purplish hue A maculopapular red dish diffuse rash was present over the lower back and at pressure points No petechiae were noted The sclerae showed a slight icteric tinge The heart was not enlarged and there were no murmurs The heart rate was 124 The blood pressure was 128/78 The abdomen protruded and was somewhat distended with slight tenderness in the left lower quadrant

The liver was palpable 3 to 4 *fingerbreadths below the costal* margin External hemorrhoidal tabs were present There was a coarse tremor of the hands and upper arms and legs with muscular twitching

Laboratory data The urine was dark amber and had a specific gravity of 1 015 to 1 028 The albumin was 4+ Sugar and ketones were negative There were 0 to 2 white cells per high power field and a few hyaline casts The uri nary urobilinogen was 1 256 to 1 512 on five determina tions Bile was always present indicated by foam test The red cell count was 3 800 000 to 2 850 000 and the hemoglo bin 9 5 to 10 02 Gm The hematocrit was 32 9 per cent The mean corpuscular volume was 87 cubic microns the mean corpuscular hemoglobin 26 micromicrograms and the mean corpuscular hemoglobin concentration 31 per cent The reticulocytes were 1 1 per cent and thrombocytes 150 000 The bleeding time was 3 minutes The white cell count was 1600 to 1250 There were 82 to 90 per cent polymor phonuclear leukocytes with many band forms The nonpro tein *nitrogen was 29 mg per 100 cc The total protein* was 4 20 Gm per cent with 3 73 Gm of albumin and 1 38 Gm of globulin The icteric index was 18 to 25 The carbon dioxide combining power was 61 4 vol per cent. The chlorides were 96 07 milliequivalents per liter The calcium was 8 9 mg p r 100 cc The nasopharynx on admission showed hemo lytic *Staph aureus* and beta hemolytic streptococci The throat contained hemolytic *Staph aureus* diphtheroids and alpha streptococci The urine contained hemolytic *Staph aureus Staph albus* and *E coli* A spinal tap showed an initial pres sure of 150 mm with normal dynamics The total protein was 36 mg There were 2 lymphocytes The sugar was 80 mg The bilirubin was 1 78 mg Cephalin flocculation was negative

X ray examination of the chest on the second day showed a few calcified hilar lymph nodes On the seventh day there was diffuse mottled infiltration of both lungs While these changes may have been due to pulmonary edema they were more indicative of miliary tuberculosis On the ninth day the findings were much less suggestive of miliary tuberculosis On the seventh day the intestines were moderately distended with gas

Course Throughout the 15 hospital days the tempera ture remained between 103 and 105 orally and was never

below 102 The pulse paralleled the temperature ranging between 100 and 140 in the first 5 days and thereafter was always above 120 The patient gradually went downhill becoming more and more disoriented until delirium set in He continued to have involuntary muscular twitchings and coarse tremors of the extremities On the third day he received 500 cc of whole blood and 500 cc of plasma with but slight improvement He was placed on a high carbohydrate high protein low fat diet supplemented by intramuscular and oral vitamins particularly vitamin B complex On the fifth day he was in a state of semicoma with delirium The respirations decreased slightly in rate from 34 with more gasping than previously and shortly thereafter the patient expired

Autopsy revealed acute massive liver necrosis as the cause of the prolonged fever

Tuberculoma of the Liver Herrell and Simpson (79) reported the case of a patient who had recurrent attacks of fever accompanied by severe pain between the scapulae Exploratory laparotomy showed the cause of the fever to be a single tuberculoma of the liver The features which suggested a lesion in the right upper quadrant were the severe pains which radiated to the interscapular region This case is discussed further below

In another group of cases there was fever, abdominal pain and leukopenia with enlargement of the liver and spleen due to tuberculosis of the abdominal lymph nodes and lesions of the liver One patient had a severe attack of abdominal pain followed by high fever and deep-seated abdominal tenderness He was found to have miliary tuberculosis of the liver at operation 3 weeks after the onset of the pain and 1 week before signs of miliary tuberculosis of the lungs were demonstrable This patient lived for 4 months after the onset of the illness Other patients with tuberculosis of the liver and spleen may have a protracted course of illness of several years duration

In short tuberculosis of the liver which is important clinically is a rare disease Nevertheless it must be considered

in obscure cases of fever especially when there are symptoms or signs suggesting disease of the liver

A solitary tuberculoma is a rather rare occurrence At the time of Herrell and Simpson's report there had been only 2 cases recorded in the literature It was known by these authors that there were three specimens in pathologic museums in various parts of the world Their patient was a 45 year old man of Turkish extraction whose complaint was chills and fever lasting 2 to 3 days and occurring every 2 to 3 weeks for 6 years His weight had decreased from 185 pounds to 136 pounds during this period In 1931 he had had an exploratory laparotomy and appendectomy without benefit He also had pain in the scapulae which was referred to the right upper quadrant An exploratory laparotomy revealed an inflammatory mass in the right lobe of the liver the size of a small grapefruit situated just to the right of the gall bladder Grossly carcinoma was suspected but cultures and microscopic section revealed tuberculosis The patient was last heard from 4 months after operation at which time he had gained weight but was still having low grade fever

Subphrenic Abscess Subdiaphragmatic inflammation with or without abscess formation is one of the causes of prolonged fever Infections in this region should be considered in any patient with prolonged fever especially under these circumstances

1 Following intra abdominal disease or an operation for local or generalized peritonitis
2 *Following disease in a neighboring organ with extension* to the subdiaphragmatic space
3 Following an infection elsewhere in the body in which an abscess appears and is apparently metastatic

In the first group, the subphrenic inflammation most often occurs after acute appendicitis a perforated gastric or duodenal ulcer or cholecystitis In the second group the suppuration or inflammation follows disease of an organ such as the liver or an infection of the lung or pleura In the third group the infection occurs most often in the anterior space, it is seen more often in children than in adults The presenting signs are often fever and a swelling in the upper part of the abdomen

Hematogenous Infection of the Subphrenic Space Cases of this disease are rare and have been described most often in children While the infection is considered to be metastatic the evidence is for hematogenous spread The history is usually that of a child with a previous infection of the upper respiratory tract otitis media or recurrent staphylococcal infection This is followed by fever and other constitutional symptoms of infection which persist and are accompanied by attacks of upper abdominal pain Within 1 to 3 months a mass appears in the upper abdomen localized on the side of the disease The x ray examination may be of corroborative value The three points of importance in diagnosis are a history of a previous infection an upper abdominal mass and recurrent attacks of upper abdominal pain

The diagnosis of subphrenic abscess is usually made from

1 The history of a previous intra abdominal disease or an abdominal operation
2 The symptoms and signs of an infection
3 Localizing signs and symptoms in the right or left upper quadrant
4 X ray examination of the diaphragm
5 Exploratory puncture

Subphrenic abscess may complicate a liver abscess and give rise to the only localizing symptoms or signs indicating the origin of an infection In these cases the symptoms and signs of an infection invariably precede the signs of an abscess

There is nothing peculiar or characteristic about the symptoms or signs of infection in these cases One should consider the possibility of a subphrenic infection when there are evidences of continued infection following an abdominal operation for localized or generalized peritonitis especially when other common complications have been excluded (pulmonary and wound infections and the appearance of symptoms and signs of infection some weeks after an acute episode suggesting intra abdominal disease)

Localizing symptoms and signs in the right upper quadrant are due to irritation of the diaphragm the collection of fluid and complications in the lung and pleura *They include* pain or discomfort in the upper part of the abdomen or in the shoulder (*phrenic irritation*) *difficulty in breathing* and hic cough all of which are exaggerated by respiratory effort as well as downward displacement of the liver tenderness on deep pressure and in extreme cases swelling and edema of the skin

The thoracic findings indicate diminished expansion with elevation and limited movement of the diaphragm diminished breath sounds over the lower lobe or the signs of a pleural effusion Since 90 per cent of all subphrenic abscesses are on the right side these signs are commonest in the right upper quadrant and the right side of the chest

X ray examination is of the greatest importance since it shows elevation and fixation of the diaphragm haziness of the diaphragmatic shadow haziness of the lung field with dis appearance of the normal costophrenic angle displacement

of the heart away from the lesion and a gas bubble with fluid level under the diaphragm (10 to 20 per cent of cases)

Exploratory puncture often establishes the diagnosis, but the ability to aspirate fluid does not exclude the possibility of an abscess since the fluid may come from the chest because of a complicating empyema In any event the pleural fluid may be sterile or may contain bacteria suggesting a subphrenic origin since colon bacilli streptococci and staphylococci are the commonest organisms

In brief the diagnosis depends on the history and the signs of an infection of the upper quadrant with or without involvement of the pleura X ray examination and exploratory puncture are most important in establishing the diagnosis

The conditions that are most readily confused with a sub diaphragmatic abscess are those that produce a high diaphragm This confusion becomes particularly great following an abdominal operation or a complicating empyema

Following any abdominal operation it has been found that the diaphragm is elevated and fixed there are diminished expansion and diminished breath sounds and impaired resonance with some haziness of the lung base due to varying degrees of atelectasis and an accumulation of air under the diaphragm (Miller *80*) Under these circumstances the clinical course and the nature of the primary disease are most important in making a decision

In the case of unilobar atelectasis the diaphragm may be high with an increased density in the lung field and a displacement of the heart to the affected side, with some narrowing of the ribs In subdiaphragmatic conditions there is likely to be a displacement of the heart away from the affected side and a hazy costophrenic angle with no narrowing of the rib spaces

The empyemas that are confused with subdiaphragmatic

abscess are those of the encysted diaphragmatic type The history is that of a primary pulmonary infection and the lung base and diaphragm are often obscured Aspiration and injection of the space with air and re examination by x ray often clear up the diagnosis It should be remembered however that empyema between the lungs and diaphragm rarely enters the subphrenic space and that a subdiaphragmatic abscess may traverse the diaphragm The latter is much commoner than the former

Left Sided Subphrenic Abscess These abscesses arise from an infection in the pelvis either a postpartum or post abortion infection a rupture of the appendix or perforation of the stomach or colon They occur only about one third or one fourth as often as subphrenic abscesses in the right side They may rupture into the bronchus pleura stomach colon peritoneal cavity or small intestine or perforate the skin The diagnosis may be difficult since symptoms and signs which are helpful in right sided abscesses may be absent in left sided ones The following points are important

1 A history of preceding pelvic infection or ruptured appendix
2 The symptoms of infection
3 Pain in the neck and lower thorax on respiration
4 Tenderness on pressure in the left upper quadrant if the abscess is a large one a mass may be felt
5 Signs of fluid in the left pleural cavity
6 Fluoroscopic and x ray signs a high fixed diaphragm and separation of the stomach from the diaphragm when the patient is placed in the low Trendelenburg position after taking barium The space may contain air An abscess in the anterior position displaces the stomach

downward medially and posteriorly If the abscess is posterior, it displaces the stomach forward

Subdiaphragmatic Inflammation In many cases of sub diaphragmatic inflammation the process subsides spontaneously without suppuration This is true in 22 to 66 per cent of clinical cases in which the diagnosis of subdiaphragmatic inflamma tion is made It is not infrequent as a manifestation of gono coccal infection in females but it is much more common in the conditions that produce subdiaphragmatic abscess The clinical features were first described in this country by Lee (*81*) who reported a group of cases in which patients had irregular fever lasting from 8 days to 4 weeks leukocytosis and symptoms re ferable to the right pleural cavity The signs were those of a high diaphragm on the right side and dullness varying with force of percussion and with inspiration The x ray always showed a high diaphragm with no process in the lungs

In a word these cases show all of the features of a sub phrenic inflammation without the demonstration of pus and recovery occurs spontaneously without suppuration

Liver abscess in the left lobe or medial part of the liver may make diagnosis difficult because it causes swelling of the concave surface of the liver Such abscesses produce an upper abdominal tumor but with no changes in the diaphrag matic shadow The diagnosis can often be suspected from x ray examination of the stomach

The epigastric tumor produced by abscess formation presses upon the stomach The symptoms and signs are dull upper abdominal pain lasting from 2 weeks to 2 months weight loss fever and leukocytosis The abscess may be secondary to amebiasis or a septic infection in the portal area

X ray examination should be made in the prone position so

that the liver is in contact with the stomach When the concave surface is enlarged there is pressure on the lesser curvature As the enlargement increases the cardia is displaced to the left and the remainder of the stomach is likewise displaced downward and to the left The duodenal cap is depressed downward and to the right

When the anterior wall of the stomach is overlapped by the tumor the stomach is displaced posteriorly especially the cardia and upper end of the fundus The more medial the abscess the more the stomach is displaced anteriorly or forward

DISEASES OF THE RENAL TRACT

The urinary tract is noted for the frequency with which it harbors the cause of obscure fever Rubin (*82*) discussing fever due to disease of the urinary tract pointed out that pus in the urine is the most important sign The pyuria of pyelitis may be intermittent and hence a single negative urine specimen does not rule out this system as the source of obscure fever Another cause is a carbuncle or multiple abscesses of the kidney This illness is usually associated with a history of infection of the respiratory tract The urine may be free of pus There is usually a leukocytosis

Tuberculosis of the Kidney This condition should also be thought of in the differential diagnosis It is rare in children White and red cells may be seen in the urinary sediment If the culture of the urine is negative guinea pig inoculation should be carried out A tuberculin skin test may also be used as confirmatory evidence that the patient has at least been exposed to the tubercle bacillus Demonstration of the acid fast organism clinches the diagnosis

Cystitis This is a rare cause of obscure fever in children A history of recurrent urinary tract infection should arouse suspicion of a congenital abnormality of the urinary tract Urinary calculi may at times lead to obscure fever without evidence of white blood cells in the urine

The subject of neoplasm of the kidney has been discussed fully in Chapter VIII (see page 159)

Cortical Abscess An infrequent cause of obscure fever due to staphylococcal infection is a cortical abscess of the kidney In many cases the diagnosis cannot be made until local signs have asserted themselves There are several reasons for the difficulty in diagnosis The lesion is situated in the cortex of the kidney, and localized signs are infrequent until the abscess extends to the perinephric tissues the pelvis of the kidney or more rarely to the renal veins Examination of the urine may be practically negative in at least 75 per cent of the cases There is a long latent period often 3 to 6 weeks between development of the original focus of infection and the symptoms of a renal abscess Pyelography may give no evidence of renal involvement and differential functional tests may or may not be helpful It may be as long as 5 or 6 weeks after the onset of fever before physical signs appear that allow one to make the diagnosis

In cases in which this diagnosis is suspected the following points in the history and examination should be observed

1 There may be a history of a staphylococcal infection 3 to 6 weeks or more before the onset of fever or of boils carbuncles sore throat or sinusitis, middle ear infections paronychia parotitism or blisters of the skin In proved cases this history is obtained in approximately 80 per cent These infections are frequently insignificant and may be forgotten by the patient

2 Pain and symptoms referable to the urinary tract (kid ney or bladder) or perirenal tissues may be absent A specimen of urine obtained by catheterization may show a few leukocytes and red cells and *Staph aureus* on culture

3 The white cell count is usually elevated to between 10 000 and 20 000 but in a few cases it is within nor mal limits In such instances the increase of polymor phonuclear cells may be significant *The absence of leukocytosis does not exclude a staphylococcal infec tion*

4 Abnormalities in the pyelograms have been found in about 75 per cent of the cases They resemble the find ings of renal neoplasm consisting of compression of the pelvis and elongation of calyxes failure to fill all calyxes and pressure and distortion of the upper part of the ureter

5 Cultures of urine from the suspected kidney may yield *Staph aureus* and the differential test may show im paired function of one kidney

In summary then a renal abscess may be suspected in a patient with a fever without physical signs if there has been previous staphyloccal infection with unilateral impairment of renal function indicated by differential test the presence of staphylococci in the urine from one side and an abnor mality of the renal pelvis indicated by pyelogram

Physical signs that should suggest a diagnosis with or without the above signs are a palpable kidney tenderness over the costovertebral space spasm of the sacrospinalis muscles slight scoliosis with concavity to the left and pain in the back or flank

Periarteritis Nodosa One rare disease of the kidney which is accompanied by fever and may be overlooked is periarteritis nodosa The presence of progressive deterioration of renal function with abnormal urinary sediment and fever especially if there are any other signs of vascular disease elsewhere should direct one s attention to this possibility

Perinephric Abscess This is often overlooked due to the fact that the physician ignores this region during physical examination Fever is that of sepsis with wide fluctuations in 24 hours Chills may be present Especially in children evidence of p oas muscle spasm may lead one to consider the perinephric area as the source of the fever

These abscesses almost invariably arise from a suppurative lesion in the kidney Rarely they occur as a result of extension of an infection from a neighboring organ as in Pott s disease of the spine carcinoma of the colon pelvic abscess retroperitoneal appendicitis and infection of the gallbladder The symptoms and signs depend in large part on the rapidity of the development of the process and the site of the original lesion in the kidney Patients present fever of obscure origin, pain in the back abdomen or lower part of the chest empyema without a preceding history of pneumonia and a mass in the abdomen or flank

Fever of obscure origin One of the areas in which an infection may be present for a period of time without giving definite localizing signs is that around the kidney In most of these cases the infection has started in the kidney and gives rise to constitutional symptoms and signs without definite localizing evidence of involvement of the perirenal tissue for at least 4 to 6 weeks The localizing signs appear when the infection spreads directly to the perirenal space

Pain in the back, abdomen, or lower chest When the abscess arises in the upper pole of the kidney and extends to the

perirenal space there may be pain in the lower part of the chest that is increased by respiratory effort such as deep breathing or coughing *There may be little or no rigidity of the lumbar or* abdominal muscles and very little costovertebral tenderness There may be impaired resonance diminished breath sounds and rales at the corresponding base of the lung and tenderness in the intercostal spaces in the axilla The lung descends on in spiration but the diaphragm is usually elevated and shows a diminished mobility As the abscess in this region increa es in size rigidity of the lumbar muscles with tenderness appears and the kidney may be pushed downward so that the lower pole becomes palpable Fluoroscopy and x ray examination of the chest noting the position and movement of the diaphragm are both helpful in the diagnosis of an abscess in this area

Abdominal pain is a conspicuous feature when the abscess begins in the lower pole of the kidney or on its anterior surface The pain is referable to the lower quadrant or to one of the hypochondriac regions There is often rigidity of the rectus muscle with tenderness and a mass may be felt in the subhepatic region or in a lower quadrant of the abdomen

Pain in the back is a conspicuous feature in cases in which the pus accumulates between the kidney and the lumbar muscles

In these cases there is rigidity of the lumbar muscles with scoliosis acute costovertebral tenderness swelling edema and redness of the overlying tissues X ray examination of the region may show a diffuse shadow sometimes obliterating the margin of the psoas muscles

Empyema Abscesses beginning about the upper pole of the kidney frequently extend upward perforate the diaphragm and produce empyema Empyema from perinephric abscesses is less frequent than that from intraperitoneal subphrenic abscesses Empyema of obscure origin especially if the organisms are staphylococci or colon bacilli should immediately arouse suspi

cion of an infection below the diaphragm extending into the pleural cavity

Masses in the abdomen or flank When an abscess of the kidney develops insidiously, the organ may become enlarged and produce a palpable mass that suggests a tumor This mass may move freely with respiration and there may be very little tenderness over it

When an abscess develops from the lower pole of the kidney a mass may be felt in the region of the appendix or in the subhepatic region and it may be mistaken for an appendiceal abscess or an abscess about the gallbladder What has been said concerning the urinary cystoscopic and x ray examinations in abscess of the kidney applies equally well to perinephric abscess It is well to recall that a perinephric abscess may be only one manifestation of a staphylococcal sepsis Other foci of infection should be looked for since they are frequent

In brief perinephric abscess is most often a complication of abscess of the kidney and in many cases the diagnosis of suppuration in the kidney is made only after the local signs of a perinephric abscess have developed

Pyelonephritis, E coli sepsis

CASE 7 A 53 year old Negress complained of chills One week before admission she caught cold associated with pleurisy pain in the left side moderate and of short duration Two days before admission she had a shaking chill with cough but no chest pain There were small amounts of non bloody sputum occasional vomiting and diarrhea three or four times daily

On physical examination the eyes were normal except for a suggestion of exophthalmos There were rales at both lung bases more on the right with moderate dullness in the right axilla and at the right lung base

Laboratory data The hemoglobin was 75 per cent on ad

mission The red cell count was 3 000 000 The white cell count was 22 800 with 80 per cent polymorphonuclear leukocytes The urine had a heavy trace of albumin and was loaded with white cells The nonprotein nitrogen was 38 mg per 100 cc The icteric index was 5 Chest plates on admission and later revealed bronchopneumonia at both lung bases A pyelogram taken 1 month after admission revealed an irregular calcification measuring 3 by 6 cm overlying the mid sacrum This was interpreted as a calcified pelvic mass such as a cyst or fluid The right kidney was low with the pelvis and calyxes moderately dilated There was a kink in the upper ureter The left kidney revealed moderate dilatation of the pelvis and calyxes The urine from the right ureter contained 2 to 5 red cells and 2 to 5 white cells In the urine from the left ureter there were many white cells in clumps and numerous red cells

Course During the first 10 days the patient had a swinging temperature rising to 103 + and dropping to normal on several occasions During the latter part of the second week the temperature ranged between 99 and 100 and frequently fell to normal The patient continued to show rales at the right lung base with moderate dullness as well as moderate abdominal distention The white cell count fell to 800 The pulse averaged 120 during the first week fell to about 100 and during the second and early part of the third week was below 100 Toward the end of the third week the patient again began to have swings of fever with a rise in the white cell count to 16 000 and in the pulse to 120 This continued into the fourth week with several short lasting shaking chills The chest signs persisted The temperature then fell to between 100 and 101 with a drop in the white cell count. Again at the beginning of the fifth week the temperature rose suddenly to 104 and both voided specimens and specimens obtained by catheter were loaded with white cells Urine culture at this time was positive for *E coli* with 106 000 000 organisms per cubic centimeter The patient continued to have a swinging temperature Sulfonamides were given followed by a sharp fall in temperature but it again rose abruptly after retrograde pyelography Two blood cultures were positive for *E. coli* soon thereafter The patient for the first time appeared extremely ill Transfusions and parenteral therapy were given The temperature again approached normal during the sixth week then rose rapidly to 103 and

104 Soon thereafter the patient went into coma transfu sions were repeated The patient became rapidly worse and expired early in the seventh week

Autopsy examination showed evidence of severe kidney in fection with *E coli* sepsis

APPENDICITIS

The cases of prolonged fever due to appendicitis are usu ally those in which the original disease has been overlooked and mi diagnosed and in which the fever is due to complica tions such as local peritonitis pylephlebitis liver abscess or subphrenic or pelvic ab cess It is the complication rather than the original disease that commands attention The ma jority of patients in whom the diagnosis is missed have atyp ical symptoms which are not especially frequent in this dis ease so that even the most careful observer may be misled

These symptoms include chills at the onset of the appendi citis diffuse abdominal pain diarrhea and pain referable to the pelvis or the upper quadrants Common features such as vomiting muscle spasm and rigidity may be absent It is well to recall that the appendix may extend into the iliac fo sa along the iliac vessels into the pelvis and to the promontory of the sacrum or it may be medial to the cecum over or under the ileum or behind the ileocecal junction behind or lateral to the cecum Inflammation of the appendix in these various positions may account in part for some of the variations in the clinical findings It is well to remember that abdominal pain and localized tenderness are the two commonest fea tures of acute appendicitis and when they are accompanied by increased tension or rigidity of the abdominal wall fever and leukocytosis the diagnosis is almost certain In the case of pelvic appendicitis the abdominal pain may radiate to the left side and give evidence of irritation of the rectum or

bladder The abdomen may be soft and tenderness may be elicited only on rectal examination In obese individuals there may be difficulty in eliciting abdominal tenderness or detecting muscular rigidity In any event, acute appendicitis must be considered first in all cases of acute abdominal pain with fever accompanied by local tenderness over the right lower quadrant.

Appendiceal Abscess In the following case an obese woman with an appendiceal abscess had anorexia loss of weight and fever A mass developed in the pelvis and operation disclosed a tuboappendiceal abscess There was complete recovery after removal of the appendix and drainage of the abscess

CASE 8 A 60-year-old woman complained of anorexia and loss of weight of 5 months duration and fever of 3 months duration Six weeks prior to admission there was on set of chilly sensation followed by a shaking chill which lasted about a half hour There was tingling stiffness, and pain in the left foot, but no redness or swelling The daily temperature fluctuated b tween 99 and 100 There was weakness fatigue and nausea An upper gastrointestinal seri s prior to admission failed to reveal any significant pathology being interpreted as consistent with a mild gastritis The chest plate indicated the resolving pneumonitis In the week before admission the temperature became less There had been a decrease in body weight from 185 to 157 pounds.

On physical examination the abdomen was very obese and poorly relaxed There were no masses or tenderness except for a small area in the right upper quadrant 4 to 5 cm below the right costal margin The liver spleen kidneys and gall bladder were not palpable There was minimal pretibial edema bilaterally There was marked tenderness on the sole of the left foot

Laboratory data The hemoglobin was 11 3 Gm The hema tocrit was 37 per cent. The sedimentation rate was 45 mm per hour The white cell count was 5400 with 57 per cent polymorphonuclear leukocytes 27 per cent lymphocytes and 15 per cent monocytes. Later it was 7100 with 79 per cent

polymorphonuclear leukocytes The nonprotein nitrogen was 31 mg per 100 cc The fasting blood sugar was 152 mg The stools were guaiac negative The alkaline phosphatase was 6 78 Bodansky units The acid phosphatase was 0 43 Gutman units

X ray examination of the kidneys showed no abnormality There was a small calcification in the left abdomen which re sembled a phlebolith An intravenous pyelogram showed early appearance and good concentration of dye The infundibula of the right kidney was elongated and narrowed and sug gested a small cyst between the superior and middle calyxes On barium enema the barium followed to the cecum without delay The terminal ileum could not be filled The cecum was irritable but no localizing mass was demonstrated The find ings were thought to indicate typhlitis

Course During the first days of observation the tempera ture ranged between normal and 101 The patient com plained of weakness and occasional upper abdominal pain On the tenth day pelvic examination revealed a polyp extending out of the cervix An exploratory laparotomy on the four teenth day indicated that the cecum was pulled into the pel vis in the right lower quadrant The right tube was adherent to a localized appendiceal abscess This was freed and the right tube was amputated Two thirds of the length of the appendix was necrotic Following appendectomy the patient continued to run fever and a wound abscess was found Four months after discharge there was no more fever

The following case illustrates how appendicitis may begin with urinary frequency chills fever, and abdominal cramps The local signs of appendicitis were obscured and the origi nal cause of the fever and symptoms was found only at operation

CASE 9 A 45 year-old man had urinary frequency noc turia and chilly sensations with sweats lasting for 5 days This was followed by generalized abdominal cramps shaking chills and temperature of 103 There were no local signs of infection One blood culture showed *Str viridans* Agglutina tion tests for brucellosis were negative The patient developed tenderness noted on percussion over the liver and compres sion of the right chest The appendix was removed and an

abscess was drained Fever and chills continued for 3 weeks when another abscess was drained The temperature then gradually returned to normal

PELVIC ABSCESS

A pelvic abscess may cause fever for some days or weeks before clear-cut signs of localized infection appear This is essentially true in cases of pelvic infection arising from an appendix in which the usual symptoms and signs of appen dicitis have been absent or obscure or in cases of infection arising from a focus in the internal genitalia or from diver ticulitis The symptoms result from the presence of an infective process capable of producing a pelvic abscess exten sion of the infection to neighboring organs and a pelvic mass

Pelvic abscesses may be intraperitoneal or extraperitoneal or both depending on their mode of origin The extraperitoneal abscesses are the ones most likely to give rise to difficulty in diagnosis since the source of the infection may not be clear and an abscess may develop without the primary lesion having been a prominent feature In general pelvic abscesses are localized between the rectum and the bladder in the prostate and seminal vesicles in men between the uterus and bladder or in the broad ligaments in women (deep pelvic or superior pelvic or pelvirectal abscess) or between the rec tum and sacrum (posterior pelvirectal or retrocecal abscess) or in the ischiorectal fossa All these areas should be examined in any patient with obscure fever and vague symp toms referable to the pelvic region Abscesses arising in the pelvis may point about the lower pole of the kidney in the inguinal region the ischiorectal fossa rectum vagina blad der or peritoneum and in some cases there may be symptoms and signs of a generalized infection

Etiology The causes of pelvic abscess are as follows

Intraperitoneal

1 Gonococcal or puerperal infection of the pelvic organs
2 Appendicitis
3 Diverticulitis or carcinoma of the colon
4 Following perforation of a hollow viscus (peptic ulcer or gallbladder disease)
5 Pneumococcal abscess
6 Infections of pampiniform plexus or cellulitis of the thighs

Extraperitoneal

1 Following
   a Prostatic abscess
   b Instrumental trauma such as that from post urethral indwelling catheters
   c Pelvic operations (especially after a punch or cutting operation on the neck of the bladder)
   d Radium implantations of the prostate and bladder mucosa
   e Hemorrhoid operations
2 Diverticulitis of the bladder
3 Osteomyelitis of the pelvic bones
4 Infections or tumors arising in pelvic organs

Symptoms and Signs The symptoms and signs suggesting a pelvic abscess are due in part to the primary lesion and in part to an irritation of adjoining structures The common ones are

1 A sense of fullness in the rectum or perineum tenesmus and diarrhea.

2 Urinary frequency and a sense of incomplete emptying of the bladder sometimes with pyuria
3 Local tenderness in the perineum or pelvis
4 A palpable mass in the rectum or vagina in the region posterior to the bladder the perinephric region or the inguinal region
5 Abdominal distention
6 Signs of peritoneal irritation
7 Generalized sepsis with metastases to lungs

Supralevator Abscess Infections arising in the mucocutaneous line of the anus and carried by lymphatic drainage to the supralevator space may cause pelvic abscess The symptoms and signs are prolonged fever pelvic pain low intestinal obstruction and a perirectal mass Male patients frequently have symptoms of obstruction of the bladder neck with difficulty in voiding Women do not have urinary symptoms

Diseases of the Prevesical Space (Space of Retzius) Diseases in this area are infections transmitted from the bladder, urinary infiltration inflammation from a ruptured bladder inflammation from necrosis of the symphysis pubis and exostoses fibroid tumors and cysts It is well to recall that an appendiceal abscess or a pelvic abscess may point here so that an abscess pointing above the symphysis is by no means sufficient to make the diagnosis certain

In males the primary focus is most often in the bladder In women it is uterine or periuterine an abscess here may be an extension of phlegmon of the broad ligament or of the cellular tissues of the iliac fossa developing after pregnancy Injuries to the symphysis pubis during labor or symphysiotomy are important

Diseases of the bladder that are important are rupture cys

titis and urethritis Diseases of the symphysis include inflammation and necrosis Diseases of the uterus include suppurative disease of the uterus or adnexae and rupture of the cervix phlebitis in an infant and perirectal phlegmon

The symptoms may be divided into two stages local and general disturbance with intestinal and vesical symptoms, and formation of the tumor above the symphysis

The onset is usually characterized by violent colic constipation or diarrhea a sense of weight in the pelvis nausea and vomiting Within 3 to 10 days after onset there is a distinct induration above the symphysis with the tumor extending upward with its base below The tumor extends on either side of the linea alba and is either fluctuant or indurated

If an abscess forms and is not evacuated there is pelvic pain and tenesmus and the abscess may point above the symphysis at the umbilicus or down in the vagina The risk is rupture into the peritoneum The abscess may open in the bladder small intestine rectum or cecum

A prevesical phlegmon may be confused with a subumbilical abscess or a tumor or phlegmon of the abdominal wall in which cases the abscess does not extend to both sides of the linea alba A tumor or abscess in front of the uterus can usually be detected by bimanual examination

SUMMARY AND CONCLUSIONS

In this chapter the common infections that are likely to cause prolonged fever have been discussed They include tuberculosis septic infections (including bacterial endocarditis) abscesses of the liver and subphrenic space infections of the kidney and perirenal space and pelvic abscesses

When tuberculosis infections cause prolonged fever and the location of the infection is difficult to determine the

Fallopian tubes the liver the lymph nodes the pericardium and disseminated tuberculosis should be considered as possible sites

Infections of the heart valves may cause some difficulties in diagnosis if patients with this disease are treated inadequately with antibiotics

Infections of the liver subphrenic space or perirenal space and pelvic abscesses may continue to cause fever in spite of antibiotic therapy

CASE 1 A 36-year old woman complained of recurring chills of 2 weeks *duration* Two weeks before admission she developed fever chills sweats and a mild sore throat From then until admission she was prostrated in bed having repeated severe shaking chills lasting from 15 to 90 minutes coming on from one to three times daily and always followed by severe fever and then severe sweats There were no localizing symptoms except a moderately severe headache For 5 days the patient had had a moderately stiff neck

Physical examination revealed an acutely ill woman with slight jaundice The eyes showed haziness of both disk margins There was moderate stiffness and rigidity of the neck without tenderness of the glands or muscles On percussion the heart was found to be within the mid-clavicular line The heart rate was regular and slightly rapid There was a short high pitched systolic murmur at the apex and at the base Deep tendon reflexes were absent even with reinforcement Vibratory sense in the ankles was impaired The blood pressure was 100/40 the temperature 100 6 the pulse 92 and the respirations 22

Laboratory data The specific gravity of the urine ranged from 1 008 to 1 028 There was no albumin except in three specimens There was no sugar There was a 4+ bile on admission The hemoglobin ranged from 65 to 89 per cent and the red cell count from 3 800 000 to 4 900 000 The white cell count was 13 800 on admission rose to 15 000 and then fell slowly to 8800 The polymorphonuclear leukocyte percentage ranged from 82 to 96 per cent with 5 to 16 per cent lymphocytes and 0 to 6 per cent monocytes The icteric index was 20 on admission 25 on the fourth day 12 on the tenth day and 5 on the 25th day The urobilinogen was 1 128 Four blood cultures were negative Culture of bloody nasal secretion on the fifth day grew out *Staph aureus haemolyticus* Lumbar puncture on admission revealed an initial pressure of 215 which dropped to 150 on the tenth day The fluid contained 39 white cells 98 per cent of which were polymorphonuclear leukocytes The Pandy reaction was 3 polymorphonuclear leukocytes with 54 mg per 100 cc total protein The spinal fluid sugar was 63 mg per 100 cc No infective organisms were seen on smear The total protein was 29

Course The patient had a high septic temperature for 6 days varying from 100 5 to 104 0 and then a constant

temperature of 100 for 3 weeks followed by a gradual fall to normal with occasional rises to 99 2 for 6 weeks The blood pressure rose to 150/95 in the fifth week and to 130/70 in the seventh week and thereafter The impression on the second day was pyemia or septicemia with metastatic brain abscess with the primary focus perhaps in the liver On the forty fourth day the clinical impression of the neu rological consultant was a small well walled-off abscess in the left parietal region or thalamus

The pulse remained between 90 and 100 for 3 weeks then slowly rose to 120 in the fifth week and fell to 80 to 90 in the last 3 weeks No focal source of the infection could be found There was a mild aseptic meningitis which was considered to be secondary to either a systemic infection or a brain abscess The patient was treated with repeated lumbar punctures She improved slowly after the first week but re mained prostrated in bed for 2 months

At the beginning of the fourth week the patient com plained of numbness and weakness of the right arm and leg There was mild right central facial weakness and doubtful hyperreflexia on the right side without Babinski signs These findings persisted but were minimal at the time of discharge The patient was discharged improved 3 months after admis sion

The diagnosis was fever of unknown origin with aseptic meningitis jaundice and secondary anemia The probable cause of fever was brain abscess in the left parietal or tha lamic region

INFECTIONS OF THE HEAD AND JAWS

Sinusitis One should always consider an infection of the sinuses as a cause of prolonged obscure fever when there are no localizing signs or symptoms Involvement of the sinuses often escapes suspicion especially when the fever is accompanied by chills In such cases only after the usual diagnostic measures have been performed is attention focused on the upper air passages In 1937 Sohval and Som (*83*) reported 9 cases in which there was *rapid response to local therapy* The oldest patient was 42 years

of age, with the average age the early twenties The chief com plaint of Sohval and Som s first patient was low grade fever of 3 years duration

Oral sepsis Oral sepsis is occasionally the cause of pro longed fever The following is an illustrative case

CASE 2 A 30 year old woman had relapsing fever gen eralized aches and pains in the muscles and recurrent cervi cal adenitis A year later a small tender lymph node at the tip of the right mastoid bone was removed The pathologic examination revealed a sebaceous cyst and a lymph node with recent inflammatory reaction The patient continued to have recurrent fever up to 101 aching in the muscles weakness intermittent episodes of diarrhea and marked ab dominal distention Small tender lymph nodes were observed in the neck and axillae

Over a period of years the patient s condition improved gradually There were occasional remissions of fever lasting 2 to 3 weeks but relapses were associated with marked sys temic symptoms In one winter she lost 20 pounds in weight and became extremely weak with a rise in temperature al most daily to 102 Thereafter there was again gradual im provement Two years later the patient was given a course of 40 000 units of penicillin every 3 hours for 8 days without effect

In the course of 3 years several teeth were removed X rays taken before and after extraction showed no abscess or localized rarefaction of bone Five years later an impression was made of both jaws for a new partial plate following which there was an acute increase in the systemic symptoms and a rise of temperature to 101 for a few days Several small splinters of bone were then extruded together with small drops of pus There was immediate improvement with a fall in temperature Thereafter the patient gained steadily and became afebrile

INFECTIONS OF THE NECK

Thyroiditis Both hypothyroidism and hyperthyroidism have been reported to cause obscure low grade fever In 1927

Lee (*84*) reported the case of a 41 year old woman who had an afternoon fever between 99 and 100 with lassitude and spent a year in bed as a tuberculosis suspect Two years later with the fever still persisting a search was made for a focus of infec tion in the sinuses teeth and kidneys The stools were normal The patient was finally placed on 0 1 grain of desiccated thyroid extract twice daily which was gradually increased to 1 grain daily with cessation of fever On the withdrawal of thyroid the fever and lassitude recurred The basal metabolic rate was —10 to —20 When last seen the patient was receiving 1 5 grains of thyroid ix times a week and 3 grains once a week and was feel ing well

Moehlig (*85*) reported cases of hyperthyroidism with fa tigue excessive perspiration rapid heart action weight loss and fever in which a diagnosis of tuberculosis was enter tained Some of the patients had normal basal metabolic rates Cough from pressure of the goiter on the trachea was a common symptom Within a week of thyroidectomy the pa tients were afebrile

Thrombophlebitis of the Peritonsillar Veins An infre quent cause of prolonged fever often associated with chills and having few local signs is thrombophlebitis of the deep tonsillar veins The important features in diagnosis are as follows During or following an attack of acute tonsillitis there is an abrupt onset of chills fever and sweats and tenderness at the angle of the jaw with moderate enlargement of the lymph nodes In some cases the tenderness extends along the anterior margin of the sternomastoid muscle There are often signs of metastases in the lungs joints or subcutaneous tissues The thrombophlebitis may involve not only the deep tonsillar veins but also the common facial posterior facial ascending pharyngeal or internal jugular veins The thrombophlebitis is unilateral more often than bi

lateral One of the striking features of the illness is the severity of the symptoms in the face of a local lesion in the throat that appears to be healing or indeed is completely healed

The diagnosis can be made with a reasonable degree of assurance if a patient with angina develops chills and tenderness at the angle of either jaw, and if metastases occur the diagnosis is almost certain

DISEASES OF MUSCLES

Muscle abscesses arise during various bacteremias especially staphylococcus streptococcus pneumococcus and typhoid bacillus infections In many cases these abscesses are multiple but not infrequently only one muscle is involved The common muscles affected are the iliopsoas, pectoralis major, thigh and calf muscles and rectus abdominalis Rupture of the muscle fibers with a hematoma secondary to trauma or Zenker s degeneration such as occurs during the course of typhoid fever, epidemic influenza and pneumonia seems to predispose muscle to localized infections The injection of caffeine solution or other irritating substances into the muscle during the course of infection likewise influences localization These abscesses may arise by extension of infection from a neighboring structure such as an osteomyelitis of the ribs causing abscess formation in the muscles of the thoracic wall or actinomycotic infection of the muscles

Subpectoral Abscess Following infections of the finger or the radial aspect of the forearm infection may pass directly to the pectoral nodes along the lymphatics accompanying the cephalic vein This may take place without any evidence of infection of the epitrochlear or axillary lymph nodes Such infections are usually due to the hemolytic streptococcus or *Staph*

aureus The onset is usually abrupt with a high fever and all of the attending symptoms and signs of an acute infection The only localizing sign may be intense agonizing pain in the intra clavicular region increased by movement of the arm and by deep breathing In a case seen several years ago the initial provi sional *diagnosis was pneumonia with pleurisy* Examination of the pectoral region usually reveals some induration and increase in tension over the whole region from the clavicle toward the axillary fold Pain is much more conspicuous than the over lying tenderness and there may be no enlargement of the axillary lymph nodes As the disease progresses the swelling and tender ness over the pectoral region become more striking and the abscess finally points in the axilla Since the constitutional symp toms and signs at the beginning may be out of proportion to the localizing *signs of infection such diagnoses as pneumonia or* pleurisy are frequently entertained It must also be remembered that osteomyelitis of the rib may point in the subpectoral region

Abscess of the Rectus Abdominalis This is seen most often following typhoid fever pneumococcus infections or epi demic influenza Occasionally it occurs after tetanus In the above infections a hematoma of the rectus abdominalis muscle becomes secondarily infected giving rise to pain swelling and tenderness Sometimes a palpable area of induration or a mass can be felt Occasionally abscesses in this area arise from osteo myelitis of a rib or by extension from the abdominal cavity

Abscess of the Psoas Muscles Most abscesses of the psoas muscles have their origin in the spine and are due to tuberculosis The iliopsoas muscle may be the site of a pyogenic infection which does not arise in the spine but occurs as a result of di rect extension from an infection in the immediate neighborhood of the muscle or as a metastasis in bacteremia This muscle is

one of a group involved in Zenker s degeneration following typhoid fever influenza and pneumonia For this reason hem orrhage into the muscle with secondary infection can arise Common microorganisms found in these cases are *Staph aureus* hemolytic streptococci *E coli* and pneumococci According to Baer *et al* (86) pyogenic abscesses of the psoas muscles have been observed in suppurative myositis of the posterior ab dominal wall re ulting from a metastatic infection or from an infected hematoma infection of solid viscera such as the kidney retroperitoneal infections originating in the hollow viscera or those produced by extension from the peritoneum infections of the internal genitalia pleural empyema, and retroperitoneal lymphadenitis Cases have also been reported of pyogenic ab-scesses arising from diverticulitis of the colon or an iliopsoas abscess

The type of psoas abscess that is likely to remain obscure for some time or to be confused with an infection of the kid ney is that resulting from a metastatic staphylococcal lesion of the skin Several cases have been observed in which a diagnosis of arthritis was made before definite localizing signs of suppuration in the psoas muscle appeared Aside from the symptoms and signs of infection with high leukocytosis pain finally appears on the affected side beginning in the loin and in the costovertebral angle later extending downward to the iliac fossa the groin the hip joint or even into the an terior aspect of the thigh Tenderness may be detected over the same area and pain is greatly exaggerated by extending the thigh Flexion of the thigh on the abdomen gives relief and is a very common and important sign of psoas abscess Pain may not occur for some time after the on et of the infection and the same is true with the development of a mass above Poupart s ligament There may be a curvature of the spine with the convexity away from the affected side By pyelog

raphy the kidney and ureter may be displaced by the deform ity of the psoas muscle and the flat plate of the abdomen may show haziness or absence of outline

Since all these signs may be present in a perinephric abscess they are not absolutely diagno tic of an abscess in the body of the psoas muscle The following should suggest pres ence of a pyogenic abscess

1 History of a recent infection of the skin followed by fever leukocytosis and *symptoms and signs of infection* with pain present in the areas described and exaggerated by extending the thigh
2 A tendency to flex the thigh on the abdomen
3 The presence of a tumor mass above Poupart s ligament.
4 Negative urologic examination except for evidence of displacement of the kidney or ureter on the affected side
5 Haziness of the outline of the psoas muscle in flat x rays *of the abdomen*

Occasionally these abscesses arise from *Staph aureus* osteomyelitis of the spine and the areas of infection in the bone may be extremely small

CASE 3 A 60 year old woman was admitted to a local hospital in semicoma About 20 days before admission after a heavy day s work she felt unusually weak and tired Nine days later after a long automobile trip she developed anorexia passage of gas by rectum belching and abdominal dis tention without nausea or vomiting The white cell count was 16 000 with an increase in polymorphonuclear leukocytes The sedimentation rate was 80 mm per hour A urine speci men was negative for sugar and albumin and showed a spe cific gravity of 1 020 The urinary sediment was not consid ered remarkable Four days before admission a barium enema indicated a rotated cecum and diverticulosis of the colon Three days before admission there was increased anorexia in

creased thirst and drowsiness and respirations were increased in rate and depth The patient had had no bowel movements for 2 days There had been no fever or chills but a marked loss in weight had occurred One year before admission another physician noted anemia for which Feosol was given

The temperature on admission was 98 the pulse 120 the respirations 30 and the blood pressure 160/80 There was evidence of dehydration The fundi revealed grade 2 arteriosclerosis The knee jerks were hypoactive and the ankle jerks were absent

The patient was treated with insulin with marked improvement in her sensorium Following catheterization she began to run a low grade fever and *E coli* was cultured from the urine She was given penicillin initially and then streptomycin with the white cell count returning to within normal limits On the twentieth day she was discharged to a nursing home on 35 units of protamine zinc insulin daily Five weeks later she entered the Massachusetts Memorial Hospital complaining of pain in the right leg and left arm of 6 weeks duration

The temperature at this admission was 100 the respirations 22 and the blood pressure 140/70 The eye grounds were consistent with early diabetic retinitis There was a systolic murmur over the precordium of equal intensity in the aortic and mitral regions The liver was enlarged almost to the iliac crest and was firm and not nodular There was weakness and atrophy of the muscles of the left arm and right leg with marked limitation of motion because of pain Reflexes were absent in both knees and ankles

Laboratory data The specific gravity of the urine was 1 020 Albumin and sugar were present and the sediment contained many white cells The hemoglobin was 9 6 Gm per 100 cc The hematocrit was 32 per cent The white cell count was 14 000 with 75 per cent polymorphonuclear leukocytes The fasting blood sugar was 222 mg per 100 cc A urine culture yielded *Aerobacter aerogenes* nonhemolytic streptococci and *E coli* At cystoscopy a paracolon bacillus was isolated in pure culture from the right and left ureters X ray examination of the spine revealed osteoarthritic lipping of the anterior surfaces of the lumbar vertebrae A flat plate of the abdomen showed the kidneys to be normal in size shape and position. An intravenous pyelogram revealed a

slight right sided hydronephrosis A chest plate indicated bronchiectasis at the right lung base Retrograde pyelography confirmed the hydronephrosis

Course During the first week the fever ranged daily from normal to from 101 to 102 After streptomycin was started (1 Gm daily) on the fifth day the fever dropped to 100 By the eighteenth day it was again fluctuating to 101 and streptomycin was discontinued Throughout the rest of the course the daily fever reached 100 or 101 The patient was discharged on the thirty ninth day

The patient was readmitted with swelling of the right thigh of 1 month s duration varying in size and at times rather warm locally When the swelling was increased the temperature rose as high as 103 2 The diabetes had be come out of control Physical examination revealed that the mass was over the adductor canal

Laboratory data The urine contained only 2 to 4 white cells and otherwise was as before The hemo lobin was 10 6 Gm per 100 cc The white cell count was 16 000 with 86 per cent polymorphonuclear leukocytes X ray examination of the middle third of the femur revealed extensive mottled de calcification The height of the temperature on the first hos pital day was 102 8 On the following day an abscess was drained the causative organism being a paracolon bacillus Nine weeks after readmission the patient was discharged home with a draining sinus

Fourteen days later she was readmitted with a recurrence of fever after the sinus tract became occluded The infective organism at that time was enterococcus On the fifteenth day the diabetes was again controlled and the patient became afebrile

Abscess of Thigh and Calf Muscles These abscesses usu ally give rise to no great difficulty in diagnosis when fully de veloped If there is pain localized tenderness induration and finally fluctuation the diagnosis is clear The same organisms which are responsible for abscesses of the rectus abdominalis are responsible for infections in this area In any acute fever the muscles should be examined carefully for localized abscess for mation This is particularly important in patients who have had

symptoms and signs of previous bacteremia or if there is a source of infection from which bacteremia could readily occur

INFECTIONS OF BONE

Infections of bone may cause fever with few other symptoms or sepsis of local bone disease A variety of microorganisms may be implicated including staphylococci *B melitensis* tubercle bacilli and typhoid paratyphoid and colon bacilli In all cases x ray examination of the bones is essential The spine pelvis and long bones are involved most often

DISEASES OF THE CHEST

Infections of the Mediastinum In any case of obscure fever the mediastinum should be examined by x ray for enlarged lymph nodes tumors or infections The diseases of the lymph nodes that cause fever are tuberculosis Hodgkin s disease and occasionally sarcoid The infections are usually abscesses in the posterior mediastinum either pyogenic or tuberculous in origin or empyema of the mediastinal pleura secondary to pneumococcal or streptococcal infection of the lungs In many of these conditions the diagnosis can be made with a high degree of assurance from the x ray examination In some cases there may be no symptoms and signs suggesting mediastinal disease According to Lerche (87) infections in the mediastinum may cause symptoms as long as 2 or 3 years after an acute respiratory infection For this reason there may be no immediately preceding history suggesting this area as a source of infection causing fever

On very rare occasions an abscess of the mediastinum may arise from an abscess in the aorta which extends into

the mediastinal tissues In such cases one is dealing with a mediastinitis and it may be impossible to decide about the primary origin of the infection Influenzal or other respiratory infections are most important in the history

The symptoms depend on the nature of the primary disease and the location of the aortic lesion They are due to effects of pressure and to extensions of the process to other organs Hemorrhage is the most frequent cause of death The type of fever varies and is not diagnostic In Mills and Pinner s (*88*) case the temperature before admission was as high as 103 During the first week in the hospital with improved respiratory symptoms the maximum daily temperature decreased to 100 2 However on the eighth day it rose to 101 6° with a pulse rise of 30 By the end of the third week the temperature had gradually decreased to a daily maximum of 99 8°

Latent Bronchiectasis Bronchiectasis is usually easy to diagnose In the typical case a relatively young person has a history of recurrent attacks of pneumonia with cough and a varying amount of sputum between attacks When the sputum is large in amount it is possible to demonstrate a layering out of the constituents Hemoptysis in small amounts is often seen Not infrequently the patient is admitted to a tuberculosis sanitorium because of hemoptysis and fever and the acid fast organisms are not found Bronchoscopy and Lipiodol studies frequently show the cause of the fever to be bronchiectasis

One of the reasons that certain cases of bronchiectasis are followed as prolonged fever of unknown cause is the fact that only 75 per cent of cases suggest this entity on a routine chest x ray (Rickles *89*) In some of these cases cough is not a prominent symptom

Another group of young people may have only a history of

recurrent pleurisy associated with general malaise A friction rub may be the only positive physical finding, according to Smart (*90*) According to Scarlett (*91*), 43 per cent of cases have had a diagnosis of chronic bronchitis with question of pulmonary tuberculosis asthma or lung abscess before the age of 15 years In middle aged persons with obscure fever who have such a history and no recent symptoms of the respiratory tract a diagnosis of bronchiectasis should at least be considered

Kinney (*92*) studied 59 cases of bronchiectasis seen in 9754 admissions to a naval hospital and pointed out that bronchiectasis is the second commonest cause of chronic disease of the lung In a few patients there was no previous history of pulmonary disease in others there was a previous history of pneumonia asthma scarlet fever whooping cough measles lung abscess or poisoning from gas inhalation Cough was the commonest presenting symptom

An illustrative case of recurrent fever seen in this condition is that reported by Maytum (*93*)

CASE 4 A 60 year old man complained of recurring chills followed by fever to 102 and 103 lasting for a few hours for the preceding 40 years He had pneumonia at the age of 18 and again at 23 At 29 years he had typhoid fever Immediately afterward cough developed and the sputum was blood tinged

X ray examination of the lungs showed some fibrosis at both lung bases The findings were thought to be too minimal for the amount of fever exhibited However after observing one attack bronchial obstruction was suspected from the appearance of rales Bronchoscopy was then carried out Improvement resulted but febrile episodes continued and were often followed by an increase in cough and sputum It was believed that the febrile episodes were the result of bronchial obstruction with retention of bronchial secretion

ABSCESS OF THE SPLEEN

An abscess of the spleen may follow a pulmonary infec tion enteric fever or a hemolytic streptococcal infection of the skin or throat Fever leukocytosis splenomegaly with or without *pain in the shoulder or left upper quadrant or* signs of peritoneal irritation due to extension of the infectious process beyond the capsule of the spleen should suggest ab scess of the spleen In the rare cases without splenic en largement pain in the left upper quadrant in a patient with a history of puerperal sepsis enteric fever or one of the other infections mentioned above may suggest the diagnosis

REGIONAL ENTERITIS

At times an uncommon disease of the gastrointestinal tract namely regional enteritis may give rise to obscure fever Therefore a study of the small bowel may give one the lead to a specific diagnosis in rare cases The following case is illustrative of the condition The diagnosis was not reached for two years

CASE 5 A 59 year-old man complained of loss of energy and five attacks of steady substernal pain during the preced ing year together with watery diarrhea Five years previously he had diarrhea The stools were watery There was never any accompanying pain or tenderness One year before admission following a large meal he felt pressure and pain below the costal margin in the midline anteriorly Seven months before admission he was placed on a fat free diet He was told at that time after x ray examination that he had two gallstones For 2 or 3 months prior to admission he had crampy aching in the mid abdomen just above the umbilicus Physical exam ination revealed no abnormalities

Laboratory data The urine was normal The hema tocrit was 43 5 per cent the hemoglobin 13 9 Gm and the mean corpuscular hemoglobin concentration 32 7 per cent The white cell count on admission was 13 000 with 59 per

cent polymorphonuclear leukocytes The icteric index was 7 5 One stool showed a 2+ guaiac reaction X ray examination of the gallbladder (intravenous) revealed good concentration of dye with four discrete negative shadows The gastrointestinal series showed a normal stomach There was a loss of the normal mucosal pattern in the small intestine with clumping of the barium and stasis in loops of the ileum This was thought by the radiologist to be consistent with a chronic deficiency state re embling sprue

Course The rectal temperature was 100 4 on admission but thereafter remained below 99 4 The patient was asymptomatic except for pain in the right shoulder relieved by aspirin He was discharged on the fifth hospital day

The patient continued to feel tired and exhausted He was readmitted 1 month later following the onset of severe generalized crampy abdominal pain most marked in the right upper quadrant accompanied by vomiting of bile stained fluid and by diarrhea The pain was relieved only by morphine sulfate The temperature was 101 and the blood pressure 124/70 The patient appeared to be dehydrated The liver was palpated 3 fingerbreadths below the right costal margin in the mid clavicular line There was slight tenderness in the right upper quadrant

Laboratory data The hematocrit was 42 per cent The hemoglobin was 14 Gm The mean corpuscular hemoglobin concentration was 33 3 per cent The white cell count was 22 650 with 75 per cent polymorphonuclear leukocytes 19 per cent lymphocytes and 6 per cent monocytes The icteric index was 12 The bilirubin was 1 01 mg per 100 cc direct and 1 52 mg total The serum amylase was 32 There were 7 or 8 red cells in the urinary sediment The temperature reached normal the morning after admission The patient had a cholecystectomy at which time the small bowel was found to be normal

Two years later x ray showed that the patient had advanced regional enteritis and he continued to have exhaustion together with low grade fever

ULCERATIVE COLITIS

Crohn and Yarnis (94) pointed out that there are a small number of cases in which abdominal pain and mild diarrhea

have escaped notice or emphasis and which are followed as cases of prolonged fever

Ulcerative colitis of the nonspecific variety is a common source of low grade fever Usually the diagnosis is made without difficulty because of the severity of the diarrhea Crohn and Yarnis cited the case of a young woman who was treated for a number of months by an ophthalmologist for keratosis and episcleritis with continuous low grade fever

The most characteristic type of low grade fever of intestinal origin with minimal local symptoms and maximal general manifestations is often seen in cases of regional or segmental colitis Other terms found in the literature to describe this condition are right-sided colitis and diffuse ileojejunitis The patient frequently has two or three stools daily without urgency and with mild abdominal pain He often presents the symptoms of a systemic disease with a low white cell count and joint symptoms Variable ocular complications and oral ulceration may be present Segmental colitis in which the diarrhea is minimal is often confused with brucellosis chronic rheumatic fever subacute bacterial endocarditis panarteritis nodosum and the Libman Sacks form of disseminated lupus erythematosus Such a case of long standing fever with multiple involvement of the joints simulating rheumatic fever for a long period of time has been described by Sprague *et al* (95)

An interesting case reported by Crohn and Yarnis concerned a 12 year-old girl whose previous history was negative except for scarlet fever Fourteen months before she developed fever and mild diarrhea The stools were loose but not bloody and there was no accompanying pain For 3 months she had been hospitalized with a temperature ranging from 99 6 to 101 1 The sedimentation rate was prolonged The hemoglobin was 60 per cent There was a mild leukocytosis (12 000 to 14 000 white cells) The barium enema was reported as showing an

irritable colon,' and all other indications of intestinal origin of the fever were dismissed The patient continued to lose weight and developed a slight tenderness in the lower right quadrant A negative sigmoidoscopy was performed Finally an x ray examination after a barium meal revealed a typical terminal ileitis involving 46 cm of the distal ileum Laparotomy confirmed the finding and after resection of the terminal ileum and ascending colon the patient was well

Another case cited by the same authors was that of a 17 year old boy who had an irregular fever at intervals for 7 years with one transient period of diarrhea Many tentative diagnoses were made for the irregularly recurrent fever Finally a barium meal revealed a diffuse inflammatory involvement of the upper ileum and lower jejunum in a granulomatous process It is readily understood why the diagnosis was missed for a long time since there was an absence of diarrhea, fistulas, perirectal abscess or joint involvement which might have led sooner to a suspicion of gastrointestinal disease

The final case reported by Crohn and Yarnis was that of a 26 year old woman who had a routine appendectomy 15 years before admission Two years later she developed erythema nodosum over the anterior surfaces of the legs which was regarded as a manifestation of rheumatic fever Three years before admission she began to exhibit a low grade continuous fever which at times rose to 104 6° The erythema nodosum recurred and 6 months later she complained of sharp abdominal pain for the first time usually at night not associated with meals or with bowel frequency At no time did she have diarrhea and her weight increased rather than diminished The blood counts were within normal range Finally a barium meal disclosed a diffuse ileojejunitis The patient subsequently developed a phlyctenular conjunctivitis Under Sulfasuxidine and Sulfathalidine administered orally the fever disappeared

and the abdominal pain ceased except for occasional slight periodic recurrences

DIVERTICULITIS WITH LIVER ABSCESS

Older patients with abdominal complaints frequently have diverticuli of the colon A possible and often overlooked complication of the resulting diverticulitis is multiple liver abscesses An illustrative case of this complication was seen before chemotherapy was available

CASE 6 A 55 year old man complained of severe intermittent girdle like abdominal pain of 1 month s duration occasionally radiating down both legs Two weeks before admission there was onset of a severe shaking chill followed several days later by attacks of vomiting The day before admission the patient again had a mild shaking chill

At physical examination the pupils were small and irregular and did not react to light There was a short apical systolic murmur There was acute tenderness in the right upper quadrant of the abdomen and the right flank with muscular spasm of the upper abdomen The liver was palpable 3 fingerbreadths below the right costal margin The prostate was boggy enlarged and very tender The blood pressure was 140 75 the temperature 100 the pulse 100 and the respirations 24

Laboratory data The urine was normal The hemoglobin ranged from 75 to 60 per cent the red cell count from 4 800 000 to 3 700 000 and the white cell count from 15 000 to 30 000 There were only 52 per cent polymorphonuclear leukocytes with 25 per cent stab forms The blood Hinton reaction was positive on three occasions The total protein was 8 4 Gm per 100 cc The icteric index ranged from 12 to 3 Urinary urobilinogen was positive in 1 2 dilution The Takata Ara test was strongly positive X ray films of the chest on the eighteenth and thirtieth days showed the lung fields to be clear with the right diaphragm elevated On the twenty second day there was evidence of bronchopneumonia at the right lung base Five days later the lung fields were clear and the right diaphragm was still elevated

Course Because of a temperature of 101 persistent pain

and tenderness and a high white cell count the patient was explored on the third hospital day Biopsy was performed on the enlarged smooth moderately firm grayish yellow liver and it was found to be normal The patient continued to have a temperature to 102° Four days after operation he developed urinary retention and a prostatic abscess which later ruptured into the urethra On the following day wound sepsis was noted During the fifth week dullness and rales were found over the right lung base but rapidly cleared During the last 2 weeks a large tender mass was noted in the right upper quadrant and right flank together with leukocytosis and a spiking temperature of 103 daily The patient was discharged 2 months after admission

Twenty four days later the patient was found in bed disoriented and incoherent and was readmitted Physical examination showed weight loss rates at both lung bases a slightly tender firm abdominal mass extending 6 cm below the costal margin in the right upper quadrant and an absence of knee jerks The blood pressure was 100/70

Laboratory data revealed urines as on the previous entry The hemoglobin was 50 per cent of normal The red cell count was 2 240 000 The white cell count ranged from 17 000 to 19 000 with 80 per cent polymorphonuclear leukocytes The icteric index was 5 The urobilinogen was positive in 1 64 dilution The Takata Ara test was positive in tubes 3 to 6 Lumbar puncture showed a pressure of only 140 mm X ray examination revealed the right diaphragm to be more elevated than previously A flat plate of the abdomen showed marked distention of the small bowel

Course The temperature was essentially normal except for slight rises to 99 On the third day there was marked abdominal distention and tympany Peristalsis diminished in spite of enemas and the patient began to vomit and grew weaker One week later a decompression operation was carried out The patient expired on the following day

At autopsy the cause of the fever was determined to be multiple liver abscesses from a diverticulitis

PERIRECTAL ABSCESS

Weisel *et al* (96) reviewed 912 cases of perirectal abscess diagnosed at the Mayo Clinic and 630 cases in which a diag

nosis of indeterminate fever was recorded In 11 cases there was obscure or prolonged fever before the diagnosis of perirectal abscess was definitely established In 4 of these cases the diagnosis was unsuspected in 7 cases it was suspected at the time of admission

The ages of the patients in the four unsuspected cases ranged from 38 to 67 years 3 patients were men Rectal pain was noted on the initial history in 3 cases the fourth patient had a rectal mass on physical examination Two patients had dysuria at some time in the course of their illness Temperature ranged from 100 to 103° in this group

In the 7 cases in which the diagnosis was suspected the ages ranged from 22 to 55 years 3 patients were men Fever ranged from 100 to 104° In 4 cases chills were followed by a rise in temperature

Weisel expressed the opinion that in the cases of obscure fever caused by perirectal abscess the involvement of the perirectal tissue was greater than that usually seen in the average instance of perirectal abscess The correct diagnosis was reached only after repeated physical and rectal examinations

PERIPROCTITIS

One other infection which may cause fever of obscure origin is periproctitis following hemorrhoidectomy or injection of hemorrhoids There may be chills and fever for a long period of time without any definite signs of localization In some of these cases there may be phlebitis of the pelvic veins Pylephlebitis or cellulitis of the pelvic tissues finally manifests itself by other signs of these infections In some cases low grade cellulitis of the perineal tissue including the scrotum finally appears

In long standing recurrent prolapse of the rectum with ulceration of the mucosa there may be chills and fever every 2

or 3 days accompanied by diarrhea This is due to periproctitis following chronic infection of the rectal mucosa Usually the diagnosis is not difficult since the symptoms of rectal prolapse are distinctive

PERICOLIC ABSCESS

Abscesses outside the colon are often undiagnosed until they rupture within the large bowel This type of abscess is usually associated with other pathology such as cancer, as is illustrated by the following case

CASE 7 A 46 year-old Negro complained of pain in the stomach Six months before admission there was onset of pain in the abdomen 45 to 60 minutes after meals There was also pain in the lower abdomen and progressive loss of appetite weight and strength Shortly before admission the patient passed blood after stools on two occasions Recently there had been some pain on defecation

Physical examination showed a slight upper respiratory infection and tenderness in the left flank The red cell count was 4 504 000 and the hemoglobin was 65 per cent The white cell count was 14 750

Course For 10 days the patient had a swinging temperature ranging from 100 to 103 *The fever suddenly stopped* coinciding with the appearance of blood in the stool X ray examination showed a filling defect of the large bowel at the splenic flexure At operation the patient was found to have a carcinoma of the large bowel with a pericolic abscess

SEPSIS OF THE THORACIC DUCT

This infection is very rare and the diagnosis is usually made by the pathologist The duct may be infected by tuberculosis bacilli hemolytic streptococci or *B pyocyaneus* Cases of pyogenic infection have been described following infection of the left arm thrombophlebitis of the pampiniform plexus, or strep-

tococcal infection of the legs and pelvic lymph nodes and after food poisoning In short the case described indicate that in fection takes place with thrombolymphangitis where there is an infection in an area drained directly by the radicles forming the thoracic duct The amazing thing is that it does not occur more often Death occurs from peritonitis generalized infection and suppurative mediastinitis From the description of cases the diag nosis might conceivably be entertained when there is an entity known to be capable of producing this condition with high fever chills sweats leukocytosis (one case developed a white cell count of 200 000) abdominal pain and distention nausea and vomiting and signs of extension of the process to the peri toneum or mediastinum Keefer has observed a case of peri tonitis following hemolytic streptococcal infection of the left hand and spread to the peritoneum via the thoracic duct In the most thoroughly reported case by DeForest *(97)* the symptoms and signs were those of a septic infection without definite localizing signs The symptoms followed food poisoning and the later symptoms were mainly abdominal

In brief a septic infection following food poisoning in which nausea and vomiting persist with high irregular fever suggest ing typhoid fever should suggest an infection of the thoracic duct In very rare cases infection of the thoracic duct may be followed by thrombophlebitis of the left subclavian and innominate veins with subsequent pulmonary infarction

CHAPTER VI

Other Infectious Fevers

Of the common nonseptic infections that are likely to cause prolonged fever rheumatic fever brucellosis enteric fever and malaria must be considered in all parts of the world Usually if the proper examinations are carried out i e bacteriologic or serologic examinations as well as the examination of the blood, the diagnosis can be established without difficulty Some general comments follow

RHEUMATIC FEVER

Rheumatic fever is a not uncommon cause of prolonged fe ver In the cases of obscure fever reported by Alt and Barker (*1*) rheumatic fever was one of the nine common causes When cases of rheumatic fever remain obscure it is generally be cause of joint involvement Therefore in any patient with an unexplained fever in whom rheumatic fever is suspected the following points are significant a recent sore throat or respira tory infection, and a previous attack of rheumatic fever or chorea Epistaxis and attacks of nausea and vomiting serve to focus attention on the possibility of rheumatic fever as a cause of malaise and fever

Physical examinations should be made repeatedly in order to search for transient evidence of erythema marginatum or sub-cutaneous nodules or to determine whether or not a heart mur

mur develops or, if one is present whether its quality is changing

Electrocardiograms are important in detecting any evid^nce of conduction prolongation and many patients show an elevated sedimentation rate with leukocytosis Salicylates may aid in diagnosis but are not in themselves diagnostic Sometimes the diagnosis is made years after the fever on finding mitral stenosis mitral insufficiency or aortic valvular disease

The height of the fever should not lead one away from the suspicion of rheumatic fever Boone (*98*) reviewed the subject of hyperpyrexia as a complication of rheumatic fever and reported the case of a 40 year old man with a temperature as high as 106°

Finkelstein (*99*) noted especially in children a low grade fever up to 100 7 occurring 2 weeks after scarlet fever for which no cause such as an infectious focus could be found He thought that this occurred in a sensitive type of individual with vasomotor irritability The fever was not influenced by the usual antipyretics or opium but often responded to a favorable climate Atropine had no effect Pilocarpine which usually lowers temperature in a normal individual frequently produced fever to 102 adrenalin caused a normal temperature Finkelstein concluded that the fever must be from a pathological vagotonia following scarlet fever Many of these cases are undoubtedly examples of acute rheumatic fever in which fever is the only manifestation of the disease

BRUCELLOSIS

Brucellosis is one of the bacterial infections that often cause prolonged fever without local signs of infection A most important point in diagnosis is that it commonly occurs in members of certain occupational groups especially farmers abattoir

workers packinghouse workers veterinarians, cattle dealers and others who have contact with cows pigs or goats Also the history of the ingestion of goat s milk or unpasteurized milk is important The disease varies in incidence from one community to another and is most prevalent in rural dwellers and in slaughterhouse workers

The diagnosis should be entertained in any person who has prolonged fever and who has been exposed to cattle hogs or goats or who has drunk unpasteurized milk The fever is likely to occur in bouts and spontaneous remissions are not infrequent

A positive diagnosis is made only by isolating the organism from the circulating blood or from a focus of infection The organism grows well in liver infusion broth and all cultures should be incubated under decreased oxygen tension in order to obtain optimum growths especially of *B abortus* Agglutination tests are valuable in diagnosis when the titer is at least 1 160 or higher and when it increases under observation Intradermal tests are not necessarily diagnostic of a present illness but when positive they indicate previous experience with the organism

Localized signs of infection occur in the spine, pelvis or long bones so that x ray examination is useful in detecting such focal areas of osteomyelitis Meningoencephalitis of a chronic nature may also be a local sign of infection The white cell count may be normal and the erythrocyte sedimentation rate not increased

ENTERIC FEVER (TYPHOID-PARATYPHOID FEVER)

Forty years ago typhoid fever was one of the commonest causes of prolonged fever Usually the diagnosis is not difficult

tions rose to 40 from an average of 28 and the abdomen became markedly distended The spleen could not be pal pated There were a few fine rales present in the area of the left lower chest posteriorly Throughout the course of the ill ness the temperature rose to peaks of 104 to 105 2 The pulse during the first 5 days ranged between 70 and 100 and then rose abruptly to 140 The patient gradually became comatose and expired on the seventh day

Autopsy examination revealed a bowel perforation in a ty phoid ulcer Blood cultures after death yielded the causative organism

CASE 2 A 52 year old Negress complained of head ache general malaise and dull aching joint pains associated with feverishness of 6 weeks duration Five weeks before ad mission she had an afternoon temperature to 103 with nausea but no vomiting She had lost 20 to 30 pounds in 6 weeks One week before entry she noted moderate sized areas of erythema nontender and nonitching localized in the palms of both hands

For 15 years the patient had had int octurnal

Course The temperature during the first 5 weeks fluctuated between 100 and 101 6 and during the next 6 weeks it ran an intermittent course between 99 and 101 After 18 weeks the temperature subsided to normal where it remained for 2 weeks During the last month it fluctuated to 99 6 The temperature was reduced for 1 day by Pyramidon but tincture of opium had no effect

Early in the course sulfanilamide was given for 12 days with no response The palm lesions which were diagnosed as erythema multiforme disappeared after 8 weeks The patient was discharged improved after 6 months The diagnosis was an atypical Salmonella infection of the urinary tract

MALARIA

The diagnosis of malaria centers around the finding of parasites in the red cells of the circulating blood Exposure to mosquitoes or a history of previous attacks of malaria chills and fever occurring daily every other day or every 2 days associated with leukopenia and splenomegaly should suggest malaria The presence of anemia mild icterus and pigmented leukocytes is also important The examination of unstained as well as stained blood films is essential in diagnosis

CHAPTER VII

Uncommon Causes of Infectious Fevers

Of the infrequent nonseptic infections that cause prolonged ever there are a number of mycotic parasitic bacterial and eptospiral and treponemal infections that we shall consider

ACTINOMYCOSIS

This infection tends to involve the mouth throat and neck he lungs and pleura or the appendix From the appendix the liver may become involved secondarily or there may be a dis seminated disease simulating miliary tuberculosis The cases that are likely to cause difficulty in diagnosis are those arising in the gastrointestinal tract or the disseminated variety The diagnosis can be established either by culture or by examina tion of tis ues

The following case is an example of actinomycosis arising in the appendix and causing multiple small abscesses of the liver subhepatic abscess and peritonitis

CASE 1 A 24 year old woman had recurrent attacks of pain in the right lower quadrant of 5 years duration Finally she had an acute attack and was admitted to the hospital where a gangrenous appendix was removed The wound healed well but a small sinus appeared in its lower end

Three months after the appendectomy intermittent fever began and an indurated mass was found in the pelvis Abdominal exploration showed an extensive pelvic inflam matory disease A large abscess and the left Fallopian tube

were removed The pathologic report was acute and chronic salpingo oophoritis Within a month the pelvic mass had re formed and was drained throu_h the vagina but an intestinal obstruction developed which was relieved by operation There was improvement for several months but the tempera ture fluctuated from 98 to 103 There was anemia and leu kocytosis (12 000 to 20 000)

The patient then developed pain and tenderness in the ri_ht lower quadrant and another sinus which had the char acteristic discharge of a fecal fistula and passed gas through the vagina She finally developed multiple draining sinuses in the abdominal wall recurrent masses in the pelvis and the signs of a subdiaphragmatic abscess She died 18 months after the appendectomy

The autopsy showed multiple intra abdominal abscesses a subdiaphragmatic abscess on the right a fecal fistula be tween the sigmoid and transverse colon and amyloidosis of the liver spleen kidney and lymph nodes All the abscesses were due to actinomycosis and a complicating mixed infec tion

CASE 2 A 20 year old boy had vague abdominal com plaints loss of weight and progressive anemia with mod erate leukocytosis for 8 months and fever for 4V months As the illness progressed the liver enlarged slightly and the right diaphragm was higher but moved on respiration After 3 months of fever the patient developed pain on the right side with a friction rub sli_ht sterile pleural effusion and moderate enlargement of the liver Surgical exploration disclosed a subhepatic abscess The course was one of pro gressive failure and death

Autopsy showed chronic appendicitis subhepatic abscess fibropurulent peritonitis multiple small abscesses of the lungs and multiple pleuritis and small areas of focal necrosis in the liver The microscopic examination of tissues showed classic actinomycosis with origin in the appendix

AMEBIC HEPATITIS

The form of amebiasis that is likely to cause prolonged fever as the outstanding feature is amebic hepatitis usually without

abscess formation These cases have been studied intensively in New Orleans by Sodeman and Lewis (*100*) and by Ochsner and DeBakey (*101*)

The points of importance in the history and physical signs are as follows

1 A history of diarrhea in about 50 per cent of cases
2 Intermittent fever with chills
3 Pain in the region of the liver and the anterior and axillary region The pain may be dull aching constant, or intermittent
4 Jaundice in 15 per cent of cases
5 Enlargement and tenderness over the liver
6 Moderate leukocytosis (12 000 to 15 000)
7 *E histolytica* in stools in 30 to 50 per cent of cases
8 Elevation of the diaphragm and decreased movement in about a third of cases

COCCIDIOIDOMYCOSIS

This fungus infection is caused by *Coccidioides immitis* It may give rise to difficulty in diagnosis when prolonged fever and a chronic pulmonary lesion are the conspicuous features of the disease Due to the outstanding studies of Dickson Smith, and others in California new light has been shed on the pathogenesis and the course of this disease For purposes of description and a better understanding of the disease it has been divided into two phases the primary benign infection and the disseminated or granulomatous form The latter has been recognized for many years and has been called coccidioidal granuloma (Winn *102*) The primary form has been studied most intensively and recognized most often during the last 15 years

Primary Infection It is now agreed that the primary infection is confined to the lung and the regional lymph nodes insofar as the clinical features are concerned The primary infection may cause few or no symptoms that are recognized as an initial infection These patients may show only a positive cutaneous reaction to coccidioidal antigen The commonest manifestations are the constitutional symptoms of an infection and local signs in the lungs such as bronchopneumonia with or without pleural effusion or cavity formation and enlargement of the peribronchial lymph nodes There may be an associated erythema nodosum When present this usually occurs within 8 to 15 days after the onset of fever and it may last 4 to 5 days and then disappear Residual areas of pigmentation may last several weeks after which there are occasional relapses of the painful nodules The course of the infection is extremely variable and it may continue to produce disability for many months without signs of disseminated disease In a few cases however the primary infection progresses and signs of a disseminated disease appear

The diagnosis is established from the history clinical features and course together with isolation of the fungus from sputum or other tissues by culture or animal inoculation Serologic tests and cutaneous reactions may aid greatly in diagnosis

There may be a history of exposure in a region where the disease has been recognized as endemic In the United States the clearly defined areas are in the southern half of California southern Arizona and western Texas The Chaco region of Argentina is another endemic area Sporadic cases have also been reported

The symptoms that should lead one to suspect the presence of the disease are those of an infection with local symptoms suggesting a disease of the lungs These are fever cough pain

in the chest and expectoration although sputum may be scanty or absent

The leading signs are confined to the chest where indications of bronchopneumonia or pleural effusion may be evident X ray examination may be most helpful While not specific, the presence of bronchopneumonia with peribronchial lymph node enlargement with or without pleural effusion and the presence of thin walled cavities should arouse suspicion especially when such signs are associated with minimal pulmonary or constitutional symptoms or signs That is to say there is a disproportion between the constitutional symptoms and signs and the extent of the pulmonary disease

One should look for signs of dissemination such as enlarged superficial lymph nodes osteomyelitis with cold abscesses and granulomatous lesions of the skin and subcutaneous tissues

The laboratory examination usually discloses a polymorphonuclear leukocytosis sometimes with eosinophilia (8 to 10 per cent) during the early course of the disease An increased sedimentation rate and a positive cutaneous reaction to coccidioidin suggest either previous experience with the infection or an active infection Serologic tests for complement fixing antibodies and precipitin tests are most helpful in the diagnosis of active infection or in suggesting the disseminated form of the disease It should be recognized that both cutaneous and serologic reactions fluctuate during the course

The definitive diagnosis is always made by isolating the fungus in culture and by animal inoculation or tissue biopsy

Coccidioidal Granuloma The granulomatous phase of this disease is caused by the blood borne dissemination of the fungus The fungus tends to localize in the lungs lymph nodes bones (ribs sternum or spine) with or without cold abscess formation in the skin and subcutaneous tissues the joints or the cen

tral nervous system, producing meningitis Also abscesses in the internal organs such as the adrenals, kidney and spleen are seen In brief this phase of the disease, which is the least common may mimic other disseminated granulomatous diseases and especially tuberculosis The diagnosis rests on the same points as described above

In short, the diagnosis of coccidioidomycosis should be suspected in any patient who has been in an endemic area who develops symptoms or signs of a pulmonary infection such as bronchopneumonia with or without pleural effusion or enlargement of the peribronchial lymph nodes fever and erythema nodosum, signs of extensive pulmonary disease with thin walled cavities in the lung and few constitutional signs of infection, or extrapulmonary signs including osteomyelitis, with or without cold abscesses cutaneous and subcutaneous granulomatous lesions and enlarged caseous lymph nodes

Serologic tests cutaneous reactions to coccidioidin and isolation of the fungus from exudates or tissues are definitive

FUSOSPIROCHETOSIS

Palmer (*103*) described a patient with a prolonged illness characterized by vague pains in the muscles and joints relapsing fever, a rash resembling German measles arthritis and pericarditis No infectious organisms were cultured from the blood but spirochetes measuring 15 microns in length and possessing three to five spirals were demonstrated many times in dark field preparations A rat was inoculated with blood from the patient and in 10 days the rat s blood contained spirochetes

Following this Williams (*104*) described 2 cases in which fusiform bacilli and spirochetes of the type found in Vincent s angina were cultured from the blood The organisms were path

epidemiologic studies have been made during the past decade by the United States Public Health Service The organism seems to be capable of producing inapparent infections or at least unrecognized illness since evidence of exposure to the fungus is available from the survey of large segments of the popula tion of the United States by means of cutaneous tests The in cidence of positive reactions varies with the part of the country from 1 5 to 69 per cent of those tested Also it is postulated that many of the cases of pulmonary miliary calcifications are the result of histoplasmosis infections Here an infection may have occurred and healed with calcification and the cause not have been discovered at the time of the acute infection The diagnosis has been made in retrospect by finding miliary pul monary calcification and a positive skin reaction to histoplasmin

The source of the infection is not apparent in all cases al though Loosli (*110*) has recently studied cases in which the infection was acquired from the inhalation of dust From the distribution of the lesions in the body it is suggested that the portal of entry may be the respiratory tract the gastrointestinal tract or the skin

The cases that are likely to produce prolonged fever are those with signs of a generalized infection resembling kala azar They are characterized by constitutional symptoms of infection fever with leukopenia and progressive anemia and enlargement of the liver spleen and lymph nodes Other localizations are an ulcerative enteritis with enlargement of the mesenteric lymph nodes acute and chronic pulmonary infections and local ab- scesses of the skin with ulcerative lesions of the oral nasal cavity Rarely the fungus involves the adrenal glands alone and may cause destruction

The diagnosis of this disease should be suspected then in any patient with one of the following clinical combinations

1 Acute or chronic pulmonary infection with fever
2 Fever hepatosplenomegaly, lymphadenopathy, anemia and leukopenia
3 Ulcerative enteritis
4 Local abscesses of the skin with or without oronasal cavity ulceration
5 Destructive disease of the adrenals (Addison s disease)

The diagnosis may be established by finding the fungus in smears of the peripheral blood in the sputum in gastric contents in bone marrow aspirations by cultivation in artificial media by animal inoculation or by biopsy of the lymph nodes or skin Serologic tests such as complement fixation and cutaneous reactions to histoplasmin are also important

By 1945 when Parsons and Zarafonetis (*111*) reviewed the literature only 71 cases of histoplasmosis had been described Darling (*107*) characterized the disease as one in which irregular fever emaciation and splenomegaly were outstanding features It was not until 1932 that the fungus origin of the disease was finally established by growing the organism from the blood stream and spleen of a 5 month old infant with the disease The disease has been described from twenty states and the District of Columbia in addition to ten countries outside the United States It has occurred in white people Negroes and mulattoes There appears to be a higher susceptibility in the Negro In children the incidence between the sexes is equal until the age of 10 when it is higher in boys Irregular low or moderate fever is present in a high proportion of cases — 47 of 49 cases collected by Parsons and Zarafonetis (*111*) Anemia was present in 44 cases A palpable liver and spleen enlarged lymph nodes and lung lesions occurred in over half of the cases Leukopenia occurred in 28 cases Ulceration of the oropharynx and skin is less fre-

quently seen The course of the illness varies from a few months to 16 years

One of the cases reported by Parsons and Zarafonetis (*111*) illustrates how a patient with histoplasmosis may present a problem of obscure fever

CASE 3 A 41 year old man was admitted with fever and weakness Eighteen months before entry enlargement of the neck was noted and a biopsy was performed The patient was given x ray irradiation with regression of the glands and felt well again Two months before admission he developed the symptoms of respiratory tract infection which persisted for a week He noted easy fatigability weakness and a dry hacking cough Shortly thereafter fever profuse diaphoresis, anorexia and abdominal distention developed He had lost 30 pounds

The admission temperature was 101 6 the pulse 88 the respirations 22 and the blood pressure 116/58 A few small posterior cervical lymph nodes were felt A single discrete soft, nontender node was felt in each axilla and several inguinal nodes were palpable Breath sounds were bronchial and rales were present The abdomen was distended with considerable tenderness in the right upper quadrant The liver extended 7 cm below the right costal margin and the spleen was felt 3 cm below the left costal margin

Laboratory data revealed a negative Kahn reaction The hemoglobin ranged from 75 to 85 per cent the red cell count from 4 000 000 to 5 000 000 and the white cell count from 2650 to 9550 On the day of death the reticulocytes were 6 5 per cent with 0 1 per cent nucleated red cells Microscopic section of the node removed a year and a half previously was diagnosed as lymphosarcoma X ray of the chest showed parenchymal changes compatible with a clinical diagnosis of lymphoblastoma Re examination 2 days before death showed a patchy disseminated infiltration in both lungs

Course The patient s illness had a downhill course with an irregular fever as high as 104 daily The pulse and respiratory rate rose X ray therapy produced no symptomatic change At autopsy there was marked evidence of histoplasmosis

KALA-AZAR

Kala azar is caused by the so-called Leishman Donovan bodies and the evidence indicates that the disease is transmitted by several species of Phlebotomus, the dog is known to be one of the main reservoirs of infection This disease is prevalent in certain areas of China India North Africa Sicily southern Italy and France and a few American soldiers acquired it in these areas during World War II

The diagnosis is established by isolating Leishman Donovan bodies from the circulatory blood from bone marrow aspirations or from liver or spleen punctures An indirect method of diagnosis is the finding of an increased total globulin and gamma globulin in the blood plasma

The following points are important

1 Possible exposure in a part of the world where kala azar is prevalent
2 Prolonged fever often intermittent with two peaks occurring daily
3 Enlargement of the liver and spleen
4 Leukopenia anemia or thrombopenia increased serum globulin hemorrhages from the nose and gums
5 Susceptibility to infections and gangrene of skin (noma)

In any patient with any of these symptoms or signs the diagnosis should be entertained and the proper tests carried out

LYMPHOGRANULOMA VENEREUM

Fever sweats headache tachycardia or relative bradycardia joint and muscle pains malaise and anorexia are frequent symptoms and in a small percentage of patients they are so severe that the minor lymphadenitis appears of little importance At times the lymphadenitis may be absent. Luger (*112*) reported

the following case of fever of unknown origin due to lympho granuloma venereum

CASE 4 A 33 year old Negro soldier had two bouts of fever lasting less than a week Three months later he was ad mitted to an Army hospital with fever which lasted 4 days He was discharged without a diagnosis after 12 days obser vation Three months later he was readmitted with head aches chills and fever of 1 week s duration The chills were true rigors preceded by nausea and vomiting and followed by long welts on the back and buttocks Slight bilateral in guinal lymphadenopathy was noted The past history included adequate penicillin and arsenical therapy for syphilis in 1945

The laboratory data included a normal white cell count and a hemoglobin of 12 5 Gm During the first 4 days in the hospital the temperature was normal The fever curve then became intermittent with morning spikes to from 100 to 102 A Frei test was strongly positive and a complement fixation test (Lygranum) was 4+ in dilutions of 1 60 Af ter the diagnosis was established by these methods the patient was given full doses of sulfadiazine for 2 weeks Four weeks after therapy was concluded the complement fixation titer was 4+ in dilutions up to and including 1 640 Two months after the beginning of treatment the patient had gained 15 pounds and felt better than he had for a year Four months after discharge the titer had fallen to 1 40 dilution

Since this disease can be treated before meningeal and other complications take place it should be considered in the differen tial diagnosis in any patient with obscure fever who has had a possible contact with the disease It also should be considered in cases of obscure fever in laboratory personnel who have worked with the virus even months before

MENINGOCOCCEMIA

In 1924 when Dock (*113*) reported a case of intermittent fever of 7 months duration due to meningococcemia 68 cases of this disease had been recorded in the literature Character istically the condition can produce the symptoms of infection

with irregular remittent or intermittent fever which may be quotidian tertian, or quartian Most patients have at some time a maculopapular or hemorrhagic skin eruption with or without nodule formation Arthritis may accompany the general symptoms of infection The primary focus is not known Occasionally the diagnosis is not made until meningitis endocarditis or other local metastatic lesions such as ophthalmitis or conjunctivitis have declared themselves Some patients have a progressive nephritis

One of the reasons that these cases are not diagnosed early is the growth characteristic of the organism Unless carbohydrate is present in the media it is completely anaerobic Even with the proper media the organism is best grown under reduced oxygen tension Today with the widespread use of sulfonamides and other acute infective agents some of these cases are undoubtedly treated successfully without the establishment of an accurate diagnosis

RAT BITE FEVER

Infections following the bites of rats mice weasels or dogs have been due to *Spirillum minus* or *Streptobacillus moniliformis* An excellent review of the etiology and the clinical features of rat bite fever was presented by Brown and Nunamaker (*114*) who pointed out that the infections caused by these agents have many points of similarity in their clinical features Both of them may occur following rodent bites although it is established that *S moniliformis* infections may occur without a history of rodent bites Such cases have been described as Haverhill fever or erythema arthriticum epidemicum

Spirillum minus Infection In the infections due to *S minus* relapsing fever is often a conspicuous feature In some cases the temperature does not reach the normal level during the

course of the disease, although it shows exacerbations over a period of several days without reaching a normal level The diagnosis is made from the history of a rat mouse or dog bite followed by a local lesion with lymphangitis a relapsing type of fever, a skin eruption leukocytosis, a positive Wassermann reaction (in 50 per cent of cases) and response to arsphen amine The diagnosis is confirmed by isolating the spirochetes from the circulating blood by inoculating mice, guinea pigs or dogs

The original wound heals completely, but within 1 to 4 weeks after the injury there is pain swelling redness and some times vesicle formation at the site of the injury In the typical case this is soon accompanied by lymphangitis and a swelling of the regional lymph nodes Occasionally there is a general glandular enlargement Accompanying these local signs of inflammation there are constitutional symptoms and signs of an infection with fever which may last 2 or 3 days, followed by a remission lasting 3 to 8 days Recurrent bouts of fever may be observed in untreated cases for 3 or 4 months some times longer There are many variations with respect to num ber of relapses and the duration of febrile and afebrile periods Thus one may see fever 1 day a week or 2 days a week for several weeks or daily for as long as 17 days

During the febrile reaction there may be a profuse erythem atous rash with macules distributed over the body or there may be nodules over the extremity which is the site of the primary lesion Arthritis periostitis perichondritis conjunctivitis epi didymitis and nephritis have been described as features of the infection

Streptobacillus moniliformis Infection This infection may follow rat bites but it has also been described as an epi demic disease possibly milk borne The prominent features are

the symptoms and signs of infection a rubella like or morbilli form eruption on the extremities especially about the wrists and ankles and a tendency to become purpuric polyarthritis coming on with a second bout of fever 5 to 7 days after the onset of the infection bacteremia and isolation of the organism from the synovial fluid

SCHISTOSOMIASIS

Pons and Hoffman (*115*) called attention to infestation with *Schistosoma mansoni* as a cause of acute or prolonged fever Their report was based on 9 cases Knott (*116*) reported the following 2 cases of fever seemingly due to *S mansoni* in patients who had been away from an endemic area for 2 and 9 years respectively

Case 5 A 24 year-old Puerto Rican woman was admit ted with fever headache nausea vomiting and abdominal pain of 3 days duration She had not lived in an area en demic for schistosomiasis for 2 years Due to her thinness pallid complexion and general condition the clinical im pression was acute pulmonary tuberculosis However the lungs were clear on physical examination The spleen was palpable but the liver could not be felt The white cell count was 5350 and the hemoglobin 70 per cent The smear for malaria was negative On the second day the feces were posi tive for hookworm but negative for schistosomes

For the first 5 days the course was marked by daily fever with remission The patient took little by mouth The spleen was noted to be increasing in size After the fifth day the fever had only slight remission and the white cell count re mained low By the fourteenth day the spleen was 4 finger breadths below the costal margin and the liver was palpable and tender *S mansoni* organisms were found under each coverslip of a stool preparation On the sixteenth day the Widal reaction was negative On the twenty first day the pa tient s condition was critical with a hemoglobin of 40 per cent She was given 0 05 Gm of tartar emetic intrave nously The next day the temperature fell to normal It had

previously ranged from 101 to 103 Except for a single elevation of temperature on the forty third day there was gradual clinical improvement The patient was discharged on the seventieth day The liver was not palpable and the spleen was reduced in size and barely palpable

CASE 6 A 20-year old Puerto Rican woman had had un explained fever 2 years prior to admission She had not been in an endemic area for 9 years Fever began again 4 days prior to admission The liver and spleen were palpable The white cell count was 10 600 The stools showed *S mansoni* Hookworm and Trichuris ova were also demonstrable There was vomiting but no diarrhea and an afternoon tem perature By the eleventh day there was some clinical im provement Tartar emetic was given on the fifteenth day The patient was discharged with negative stools on the twenty first day

SYPHILIS

With the advent of public health education concerning ve nereal disease and with more adequate shorter term therapy (penicillin) tertiary syphilis as a cause of obscure fever will become very rare Thayer (*117*) discussing fever in tertiary syphilis pointed out that remittent or intermittent fever of ob-scure origin sometimes yields immediately to antisyphilis ther apy If it does not yield within a week or 10 days the evidence is strongly against its syphilitic origin. When no evidence of a primary syphilitic lesion is seen on physical examination it should be remembered that fever may precede the rash of sec ondary syphilis by days accompanied by severe general symp-toms In tertiary syphilis especially of the liver there may be a high intermittent fever with leukocytosis suggesting an acute septic infection

Thayer referred to a case reported by Futcher (*118*) in which the patient was on the ward for 2 months as a typhoid fever suspect with generalized aching nausea vomiting, diar

rhea and weakness Bilateral thickening of the sternal ends of both clavicles indicated an old periostitis Furthermore a distinct scar suggesting a healed initial lesion was found By the fourth day of potassium iodide therapy the fever was normal and re mained there Brief summaries of Thayer s cases follow

A 48 year old man had irregular remittent and intermittent quotidian fever ranging from normal to 104 for a year and a half He complained of weakness and vertigo with some ringing in the ears His leukocytosis was variable He had an old iritis and nerve deafness He also had small ulcers of the shins Fever ceased 1 week after antisyphilis treatment

A 40-year old man was admitted with a chief complaint of general lassitude pain in the right upper quadrant and dizziness of 5 months duration He had had an irregular fever of 99 to 103 for 2 months There were signs of old tuberculosis in the right apex A Bordet Wassermann test was positive Within 3 days after the beginning of treatment there was complete and permanent disappearance of fever

A 34 year old woman had a daily hectic fever ranging from 99 5 to 100 5 for several months together with fa tigue anorexia weight loss night sweats and alternating diarrhea and constipation A Bordet Wassermann test was pos itive The fever disappeared in 2 days after the beginning of antisyphilis therapy

A 58 year old physician contracted surgical syphilis 30 years before admission followed by incomplete mercurial treatment He was observed with quotidian intermittent fever of nearly 8 months duration He also had cutaneous lesions which were papular and scaly There was immediate and complete disappearance of fever and symptoms within 2 days of antisyphilitic therapy

A 15 year-old Negress had loss of appetite daily remittent fever of 99 to 103 moderate anemia a positive Wasser mann reaction on several occasions and a positive globulin test of the spinal fluid which contained 8 cells On the nine teenth day of the illness iodides and mercury were started, with complete and permanent disappearance of the fever in 4 days

Other articles on this subject published prior to 1923 were by Janeway (*119*), Nistico (*120*), Pebart (*121*) (fever of al most 7 years duration), and Sinha (*122*) (fever of 10 years duration)

Patients of this type may be suspected of having had pul monary tuberculosis or sepsis With the routine serologic tests for syphilis now available it is probable that the diagno sis will be made early

In doubtful cases which have received incomplete therapy after other causes of obscure fever have been ruled out a course of penicillin which is routinely given in syphilis is in dicated If there is no definite cessation of fever in 1 week another cause for it should be searched for

TOXOPLASMOSIS

A rare cause of prolonged fever in adults is toxoplasmosis The source of infection is obscure Kass *et al* (*123*) re cently reported a case of toxoplasmosis in an adult and col lected the literature on the subject They point out that toxoplasmosis is being recognized with increasing frequency in children as an illness in which congenital encephalomyelitis with hydrocephalus intracerebral calcifications microcephaly, chorioretinitis, and microphthalmus are conspicuous features

The cases of acquired infection in adults may be suspected when a patient has fever and constitutional symptoms and signs of infection with a maculopapular skin eruption and local signs suggesting meningoencephalitis (confusion delir ium coma) Polymyositis (arthralgia and myalgia) myocar ditis bronchopneumonia conjunctivitis and lymphadenopathy are infrequent findings

The laboratory examinations usually disclose a normal or

low leukocyte count and albuminuria and casts Mild anemia may be present

The diagnosis is made by injecting suspected tissue or blood into mice by the intracerebral or intraperitoneal route Muscle biopsy may show nonspecific myositis The electrocardiograms may show abnormalities suggesting myocarditis and the spinal fluid may show pleocytosis and increased protein in the cerebrospinal fluid

The fever is usually remittent and varies from 99 5 to 103 or 104° The rash is maculopapular sometimes petechial and is general but spares the scalp palms and soles In this respect it differs from the rash of typhus which involves the palms and soles

The clinical features of the disease as described in adults resemble in many respects those of rickettsial disease and the two should be discriminated However the duration of toxoplasmosis in the severe cases and the failure to respond to antibiotics should aid in differential diagnosis

TICK BITE FEVER

Much interest has been centered on the tick as a transmitter of disease During army maneuvers in Tennessee in 1943 its presence was noted in a small group of soldiers admitted to an evacuation hospital who were suffering from fever malaise and headache With the removal of ticks the symptoms subsided The usual locations of the insect were the scalp neck axillary region popliteal area lower back gluteal folds and umbilicus Feder (*124*) reported 5 illustrative cases of tick bite pyrexia There was no evidence of secondary infection and studies failed to incriminate tularemia relapsing fever Rocky Mountain spotted fever or the allied group of dis

eases Within 1 day of the removal of the female of the genus Dermacentor the patients were asymptomatic and afebrile There was no evidence of paralysis such as that reported by Abbott (*125*) Therefore in the physical examination of any one with an obscure fever ticks should be carefully looked for and removed

PART THREE

Noninfectious Fevers

manifestation of cancer Anker (*130*) had the same opinion as Buhrig as did Kobler (*131*) who gave several case ex amples

In 1899 Freudweiler (*132*) analyzed 475 cases of carci noma treated in the Zurich Clinic between 1884 and 1889 Over half of the cases were cancer of the stomach, 435 were in the gastrointestinal tract Fever was present in 25 per cent of all uncomplicated cases occurring in 45 per cent of the liver cancers 26 per cent of the stomach cancers and 21 per cent of primary cancers of the pharynx and esophagus

Pedrini (*133*) in a review of the subject of fever in ma lignancy stated that two types of fever should be distinguished, one due to growth of the tumor and the other to complica tions He expressed the opinion that fever was more common in liver and pleural tumors than in those originating in other organs

Briggs (*134a*) analyzed 238 tumor cases seen at the San Francisco Hospital over a 5 year period 74 were tumor of the stomach Fever occurred in 34 per cent of the uncomplicated cases Table 2 shows the incidence of fever in uncomplicated tumors of the other organs as reported by Briggs (*134a*) He also classified the types of fever into those with isolated rises, intermittent types and continuous or septic types and pointed out the frequency of fever when metastases were present

Tremolieres *et al* (*135*) cited a case in which chills and fever simulating an acute infection were the primary symp toms of neoplasm of the adrenal cortex Olmer (*136*) gave similar examples

In Hamman and Wainwright s paper (*3*) on the diagnosis of obscure fever cases were divided into those with long continued low grade fever and those with unexplained high fever There were 2 cases of hypernephroma in the first group in the second group there were 5 cases of hyper

nephroma 1 of carcinoma of the lung 1 of carcinoma of the liver and 1 of sarcoma of the spleen

It is well then in any patient with prolonged fever without other signs of infection to consider a tumor as the possible cause Also when a patient has had a tumor removed and later develops fever a recurrence of the tumor or metastatic disease must be considered

TABLE 2

INCIDENCE OF FEVER IN UNCOMPLICATED TUMORS

Organs	*Total No of Cases*	*Fever Not from Complications No of Cases*	*%*
Stomach	74	25	34
Esophagus	16	4	25
Colon and rectum	19	7	37
Liver and biliary system	23	12	52
Lung and pleura	5	3	60
Breast	21	7	33
Uterus	41	15	37
Head and neck	32	16	50
Prostate	7	2	29

KIDNEY

Stetter (*137*) was probably the first to describe fever in renal tumors His patient had a temperature of 102 2° or higher for 2 months before operation For the first 10 days postoperatively the temperature was practically normal A complicating pericarditis then developed In the same year Marsh (*138*) described a child of 9 years with a sarcoma of the kidney whose temperature ranged between normal and 102° Physical examination revealed a large right kidney which was regarded as a perinephric abscess At post mortem examination the mass proved to be a sarcoma

In 1896 Israel (*139*) recorded the case of a 43 year old man who had remittent fever for several months At operation a right hypernephroid tumor of the kidney was found Following nephrectomy the fever promptly disappeared Anker (*130*) recorded fever in the presence of kidney tumor

Israel wrote another paper in 1911 (*140*) in which he reviewed 146 renal tumors Fever was present in 28 cases (18 per cent), 8 per cent of the cases with fever were uncomplicated by infection He postulated that a pyogenic substance is elaborated by tumor cells Berg (*141*) reviewed 13 cases of kidney tumor seen at the Mt Sinai Hospital from 1907 to 1913 He referred to his earlier review of 25 cases of renal tumors from the same hospital seen between 1898 and 1907, and analyzed the collected series under the following classifications ache and pain in the abdomen and loin, hematuria progressive weight loss weakness and anemia palpable tumor (present in 51 per cent of the first series and in 9 of 11 cases of the later series) and evidence of metastases He pointed out that there was fever whenever a large tumor was present, especially when it was growing rapidly He believed that the fever was caused either by hemorrhage or by absorption of necrobiotic matter into the circulation

In 10 patients seen by Berg there was a temperature of 99 to 100° prior to operation except for 2 patients with a fever which reached 102° After operation the temperature fell to normal in all the cases

Loughnane (*142*) reviewed 35 cases of renal sarcoma in infants and found slight fever to be the rule In only 1 case was pyuria present Voelcker (*143*) pointed out that fever was not infrequently present in hypernephroma It often lasted a week with evening rises to between 100 5 and 102° He stated that cases were known in which fever was the first recognizable feature of the illness

Fedoroff (*144*) found fever in 25 per cent of 42 cases of solid kidney tumors that he operated on Wright (*145*) reported the case of a 59 year old man who 1 month after the onset of the first symptoms of a renal tumor noticed fever of 102° each evening

Alleman and Bayer (*146*) studied 38 solid tumors of the kidney 27 of which were hypernephromas In 5 cases fever was the predominant symptom Castano and Risolia (*147*) of Buenos Aires discussed 7 cases of renal neoplasm In 3 patients between the ages of 18 and 35 years there was fever with no symptoms referable to the urinary tract 2 of these patients had fever and chills and the third had an irregular fever without chills as the presenting complaint In one case hydatid cyst of the liver was the preoperative diagnosis and in another a perinephric abscess The authors found that the fever subsided after nephrectomy The tumor of the kidney was palpable in 6 cases Four patients had pain from the onset of their illness

Lintz (*148*) reported the case of a 63 year-old woman who had lumbar pain and fever for 4 months After hospitalization the fever rose as high as 103 The initial diagnosis was pyelitis and osteoarthritis of the spine A large hypernephroma of the right kidney was removed and postoperatively the temperature was never above 99 In spite of pyuria the leukocyte count before operation was normal

Nicholson (*149*) recorded the case of a 38 year old woman who had vague discomfort in her abdomen for 2 or 3 days with an afternoon temperature as high as 104 for 2 weeks There was marked tenderness in the right side but after 3 weeks she recovered Seven months later she complained of a metallic taste in her mouth urinary frequency and pain in the right loin The temperature at that time ranged from 99 to 101° One month later the phenolsulfonphthalein excre-

tion was 22 per cent and the afternoon temperature reached 100° with vague pain in the shoulders, knees and toes Then weakness and dizziness appeared and the pain in the right loin became moderate Because of a systolic mitral heart murmur a diagnosis of bacterial endocarditis was suspected However in 2 weeks the patient was again feeling better Eleven months after the onset of symptoms x ray examination of the chest showed a broadening of the hilar shadows of the lung At that time the afternoon temperature ranged almost daily be tween 100 and 102°

The patient again entered the hospital after 18 months of fever complaining of pain in the right shoulder and chest with an accompanying severe headache A number of annular opaque areas were noted in the right chest by x ray and she was given a course of x ray radiation on a presumptive diag nosis of Hodgkin s disease Three months later a moderate de gree of anemia had developed and she was given several transfusions She then started to have weekly attacks of in tense abdominal pain which was controlled only by morphine At times she was unable to void During the last 40 days of her illness she had no fever She died after almost 20 months of fever Autopsy revealed a renal carcinoma of the lower pole of the right kidney with secondary growths in the left suprarenal gland spleen liver and lung

Fever was found by Creevy (*150*) in 2 of 17 cases of hypernephroma Three other patients had temperature higher than 100° In Ljunggren s (*151*) case a 52 year old woman had fever for 6 months Urologic investigation revealed a left renal tumor The fever disappeared after removal of the tu mor

Frank (*152*) reported the case of a 50 year old woman who had fever nausea vomiting and pain in the upper ab domen and left side for over 7 months The hemoglobin at

the end of that time was 50 per cent An enlarged kidney was noted on the flat plate of the abdomen which led to the suspicion of a kidney tumor There was no hematuria Retrograde pyelography showed the upper pole of the kidney to be the site of a tumor Pathologically it was a cancer of the kidney

McCague (*153*) investigated the case of a 47 year old woman who had had obscure fever for 1 year accompanied by nau ea vomiting and irregular uterine bleeding from mul tiple fibroids The white cell count ranged from normal to 17 750 This was the only case in a series of neoplasms which had fever as the presenting symptom However in 37 other cases in McCague s series fever was present as a complication Twenty eight cases were afebrile

Newman and Levine (*154*) studied 2 cases in which the initial symptom of a renal tumor was fever In both patients aged 56 and 58 years respectively urinalyses were normal A complete urologic investigation revealed a renal neoplasm as the cause of the fever By the time the diagnosis was made both patients had developed metastatic lesions and had failed rapidly The first patient lived 4 months after nephrectomy and the other less than 3 months

The incidence of fever in cases of renal tumors as reported by certain authorities is given in Table 3 The percentages ranged from 10 to 56

The following cases are described in order to show that fe ver may be the presenting symptom in tumors of the kidney

Case 1 A 58 year old woman had fever and weakness of 3 months duration Her course was one of progressive failure with weight loss diarrhea and progressive anuria There was dullness at the left lung base rales in the same area and signs of a small amount of fluid After 2 months the urine revealed intermittent hematuria The pyelogram revealed a defect in the upper calyxes No mass was ever felt.

Autopsy showed an epithelioma of the pelvis of the left

kidney extension to the spleen and retroperitoneal tissues hemoureter thrombosis of the left renal and suprarenal veins and inferior vena cava edema of the legs and vulva left hydrothorax bronchopneumonia cystitis acute endocarditis gallstones and ulcerative enteritis

CASE 2 A 55 year old woman complained of weakness and low grade fever Two years previously she had been admitted to another hospital with an unexplained fever and an elevated white cell count and sedimentation rate

TABLE 3

INCIDENCE OF FEVER IN RENAL TUMORS

Year	*Author*	*Total No of Cases*	*Cases with Fever*	*Per Cent with Fever*
1911	Israel (*139 140*)	146	26	18
1913	Berg (*141*)	38	12	32
1914	Loughnane (*142*)	35	Majority	—
1922	Fedoroff (*144*)	42	10	24
1923	Alleman and Bayer (*146*)	38	5	13
1923	Castano and Risolia (*147*)	7	3	43
1926	Young (*155*)	43	4	9
1929	Creevy (*150*)	17	2	12
1940	McCague (*153*)	66	37*	56

*Stated as complication

About 2½ years previously a low grade fever began accompanied by a burning sensation in the hands feet abdomen and neck The temperature was never above 99 Five months prior to admission she had onset of substernal and precordial discomfort with a feeling of fullness in the neck Two months later a tonsillectomy was performed X ray examination of the chest and agglutinations against Brucella and enteric infections were negative The white cell count was elevated and the sedimentation rate was increased The patient had had continuous weakness and aching in the lower left chest. In 2 years she had lost 50 pounds in weight

The admission temperature was 100 the pulse 94 the respirations 20 and the blood pressure 195/105 The heart

was slightly increased in size and there was a grade 2 to 3 harsh blowing systolic murmur heard best over the apex but transmitted over most of the precordium The liver was palpated 2 cm below the right costal margin There were bilateral varicose veins of the legs

Laboratory data A blood Hinton test was negative The initial urine showed 15 to 20 white cells The specific gravity was 1 026 Repeated urine examinations failed to show white cells The sedimentation rate ranged between 41 and 48 mm per hour The hematocrit was 43 per cent and the hemoglobin 13 7 Gm per 100 cc The white cell count was 14 300 with 69 per cent polymorphonuclear leukocytes and 31 per cent lymphocytes The electrocardiogram showed myocardial damage T_1 was inverted and T was diphasic

A chest plate showed an enlarged left ventricle An intravenous pyelogram showed the left kidney to be considerably enlarged The dye revealed findings consistent with a tumor of the upper pole of the left kidney

Course The patient had a low grade fever with temperature varying from 99 to 100 and burning sensations of the skin At operation a hypernephroma of the left kidney was found which had invaded the left renal vein After a few minor complications which were treated with antibiotics the patient became afebrile

CASE 3 A 55 year old woman had low grade fever without local signs for 2½ years There was an increased edimentation rate leukocytosis and a defect in the upper pole of the kidney suggesting tumor Operation showed hypernephroma of the left kidney The fever disappeared after removal of the kidney

LIVER

Primary and secondary tumors of the liver are not infrequently associated with fever and chills Also tumors of the gallbladder and bile ducts are accompanied by fever especially when there is an associated infection It is well to remember that metastatic tumors to the liver originate most often in the organs drained by the portal venous system

(stomach colon and pancreas) In the extraportal system, primary tumors metastasizing to the liver arise most often in the breast lung, and eye (melanosarcoma)

Hepatoma The following case is an example of primary hepatoma with fever and abdominal pain as the outstanding features

CASE 4 A 41 year old Negro complained of pain in the right upper quadrant of 4 weeks duration For many years he had taken beer and whisky continuously Twenty years before admission he had bilateral groin abscesses which were lanced Four years before admission there was a positive serologic reaction for syphilis and the patient received an injection of bismuth During the next 2 years he received twenty two injections of bismuth salicylate and eleven injections of Mapharsen over a period of 17 months

Four weeks prior to admission the patient felt something give in the right upper quadrant followed by a steady severe ache At the same time he noted anorexia and a feverish sensation A physician found his temperature to be 102 and gave him sulfonamides for 2 or 3 days followed by oral penicillin for the same length of time The fever decreased but anorexia continued The patient had lost 20 pounds in the month before admission

Ten days before admission the patient complained of fever The right upper quadrant pain continued A large tender liver a questionable rectal mass and positive blood serology for syphilis were ascertained Chest x ray examination revealed an elevated right diaphragm The Frei test was doubtful Proctoscopy was negative to a distance of 10 cm and thereafter the instrument met obstruction The patient was referred to the hospital with a possible gumma of the liver

On admission the temperature was 97 the pulse 72 the respirations 20 and the blood pressure 120/80 Small soft discrete nodes were easily palpated in the right posterior cervical region in the right axillary region and bilaterally in the epitrochlear region There was elevation of the right diaphragm and a friction rub at the right base of the lung laterally The liver edge was palpable 4 fingerbreadths below the costal margin with a slight bulge in the mid-clavicular

line There was also tenderness in this area To the right there was a rounded smooth nontender mass which de scended on inspiration and could be felt just above the iliac crest This was thought to be the right kidney Rectal exami nation revealed tenderness with a vague impression of a soft mass pushing the rectum posteriorly

Laboratory data A blood Hinton te t was positive The specific gravity of the urine was 1 016 There was 2+ bile Urobilinogen was present in a dilution of 1 32 The blood sedimentation rate was 43 mm per hour The hematocrit was 42 per cent The hemoglobin was 13 3 Gm per 100 cc The white cell count was 5350 with 58 per cent polymor phonuclear leukocytes 10 per cent lymphocytes 3 per cent monocytes 6 per cent eosinophils and 4 per cent basophils The bilirubin content of the blood serum was 2 76 mg per 100 cc direct and 4 62 mg total The cephalin flocculation test was 2+ The thymol turbidity was 3 0 units the protein 6 12 Gm the albumin 2 44 Gm and the globulin 3 68 Gm per cent The alkaline phosphatase was 22 7 Bodansky units Sigmoidoscopy revealed no intrinsic lesion as far as 38 cm

Course The patient was afebrile for 4 days but 3 days later the temperature rose to 104 accompanied by an in crease in the friction rub at the right base A Bromsulphalein retention test (5 mg per kilogram of body weight) showed 25 per cent remaining in the blood stream at the end of 30 minutes

An exploratory laparotomy with liver biopsy performed on the seventeenth day showed the liver to be lobular and en larged with perihepatitis The pelvis showed a small amount of icteric fluid Pathologic section of the liver tissue revealed a hepatoma in addition to portal cirrhosis The patient died after developing ascites in the fifteenth week of his illness

GALLBLADDER AND BILE DUCT

In 1889 Musser (*156*) reviewed 100 cases of carcinoma of the gallbladder and 18 cases of carcinoma of the bile ducts In his first case of tumor of the gallbladder the initial symp tom was an intermittent fever occurring between 1 and 8 P M with peaks at 103° The diagnosis was primary carcinoma of

the gallbladder, hepatic colic, pain in the right hypochondrium jaundice enlargement of the liver fever, vomiting and diarrhea Death was attributed to exhaustion Musser thought that in some cases fever commenced at about the middle of the di ease and continued to the end It could be either intermittent or continuous and he believed that it was always due to the presence of inflammatory complications

In the 18 cases of carcinoma of the bile ducts fever was recorded at some time in the cour e of the disease in 7 In 4 cases it was intermittent in 1 it was irregular and in 2 cases the type of fever was not described Musser cited Delafield s report of 5 cases of carcinoma of the bile ducts in 1 of which fever from a suppurative inflammation of the bile ducts was a presenting symptom

BONE

Tumors of bone either primary or metastatic not infrequently cause fever and in many instances it is periodic or relapsing The two primary tumors causing fever most frequently are Ewing s sarcoma and multiple myeloma Ask Upmark (157) analyzed a number of ca es of tumors and other diseases of bone associated with periodic fever He listed primary and metastatic tumors of bone as well as lymphogranuloma and leukemia as the common tumors of bone associated with fever It is important then to examine the blood for signs of leukemia or myeloma and to x ray the bones when a primary or secondary tumor of bone is suspected as a cause of prolonged or relapsing fever

LUNGS

A small number of patients with latent tumor of the lung show fever as a primary presenting symptom together with

nonspecific complaints such as weight loss and fatigue Mc Crae (158) found fever at some time in 55 per cent of a series of cases of bronchial neoplasm Funk (159) found fever in 55 per cent of 61 patients but thought that it was due to bronchitis pulmonary suppuration bronchiectasis bronchopneumonia or pleurisy He pointed out that the fever might be slight or marked with remissions and intermissions and with chilliness and sweats

Maxwell and Nicholson (160) studied 100 cases of bronchial carcinoma The symptoms were of sudden onset in 25 cases and insidious in 75 In the majority of cases the initial symptom involved the chest but on some occasions the local condition remained quiescent and attention was drawn to it only by the occurrence of symptoms as a result of metastasis As to temperature the author believed that it was difficult to convey any exact impression since so many factors influenced the form of the temperature charts from stage to stage of the disease Fifty seven patients were afebrile thoughout their course In 31 cases the temperature was 100 or less The chart did not appear to bear any strict relation to the degree of acute inflammation Even in the presence of pus there was not necessarily fever It was noted that fever could occur in cases of bronchial carcinoma without the finding of inflammatory changes at postmortem examination

STOMACH

Kratschmer (*161*) reported a case of cancer of the stomach which was probably far advanced and in which fever was a prominent feature Hampeln (*162*) pointed out that a high septic fever with chills and fever lasting a long time and simulating malaria could be caused by carcinoma of the stomach Finlayson (*128*) also described fever and shivering in

cases of neoplasm of the stomach Kast (*163*) reviewed the German literature and mentioned 5 cases with cancers of the stomach of varying size 1 with metastases to the liver, in which no cause of the fever was demonstrable except the tumor Fever was intermittent and was sometimes accompanied by chills

Freudweiler (*132*) found that 26 per cent of patients with gastric carcinoma had fever at some time during the clinical course Anker (*130*) described a 54 year old woman with carcinoma of the stomach without evidence of inflammation but with chills and fever Osler (*164*) stated that in tumors of the stomach the temperature was usually normal He added

> However interesting paroxysmal elevations of temperature and definite chills with fever in which the thermometer registers 103 or 104 followed by profuse sweating are reported The rigors may recur at intervals for weeks and if no tumor is felt may complicate the diagnosis In a case at the Philadelphia Hospital the paroxysms recurred for more than six weeks The autopsy showed a cancer of the stomach with adhesions to the colon and extensive suppuration at the base of the cancer and in a pocket between the stomach and omentum

Osler and McCrae (*165*) stated that fever occurred in 49 per cent of 150 cases of carcinoma of the stomach Friedenwald (*166*) reviewed 1000 cases of cancer of the stomach. Of the 472 cases in which the symptoms were noted during almost the entire course fever occurred in 203 cases (43 per cent) In 73 of these the temperature ranged between 99 and 100° in 66 between 100 and 101° and in 45 between 101 and 102 Thirty seven patients (18 per cent) had fever during the entire course of the disease 52 patients (26 per cent) developed it during the first 6 months and 151 (74 per cent) developed it after the sixth month

Smithies and Ochsner (*167*) quoted the Fenwicks as stating

that approximately one third of gastric cancer patients have some temperature elevation Of their own series of 79 cases 15 per cent exhibited fever

Rovsing (*168*) reported 2 interesting cases One of the patients had malaria like paroxysms for nearly 4 years before carcinoma of the pylorus was discovered during an exhaustive study Resection of the tumor led to cessation of the fever The other patient manifested chills fever and sweats for 4½ months before gastric symptoms appeared Subsequent resection led to restoration of health

Portis (*169*) reported the case of a 46 year old man with chills fever and pain in the lumbar region due to a metastatic lesion to bone from a carcinoma of the stomach Briggs (*134a*) reported the case of a 59 year old laborer seen 2 years previously who had malaise weakness a weight loss of 25 pounds in 4 months and upper abdominal pain For several months the patient had a daily temperature between 96 8 and 103 2° He was found to have an inoperable tumor of the stomach and died 1 month after exploration with complete pyloric stenosis

Crohn (*170*) gave fleeting consideration to pyrexia in gastric carcinoma Archard (*171*) wrote on the septic or malarial type of fever which he had seen in carcinoma of the stomach Eusterman and Wilbur (*172*) discussed a case of carcinoma of the stomach with brain metastases in which there was more or less regular intermittent fever associated with chills and sweats simulating malaria At post mortem examination acute pneumococcal type 3 endocarditis was found in addition to the tumor Masselot (*173*) reported a case which had been followed for 26 months with periodic septic manifestations only a few months before death did the patient develop mild gastric symptoms Rhea (*174*) reported a case of gastric cancer simulating typhoid fever

Starkey-Smith (*175*) reported a case of carcinomatous gastrocolic fistula simulating enteric fever Singer and Shabat (*176*) reported a case with chills fever, and sweats Autopsy revealed a suppurative arthritis of the lumbar spine with bilateral psoas abscesses The source of the infection was an ulcerative medullary carcinoma of the mid portion of the greater curvature of the stomach

Singer and Steigmann (*177*) described 4 cases of carcinoma of the stomach in which the initial clinical features were fever and its concomitants The patients were all between 51 and 63 years of age One case was thought to be subacute bacterial endocarditis another undulant fever and lung abscess the third malaria and the fourth patient was initially treated for influenza In the last 1000 cases at the Cook County Hospital the incidence of substantial fever in carcinoma of the stomach was 35 per cent

The incidence of fever in cases of gastric carcinoma as reported by some of the above authorities is given in Table 4 The frequencies ranged from 15 to 49 per cent

TABLE 4

FREQUENCY OF FEVER IN GASTRIC CARCINOMA

Year	*Author*	*No of Cases*	*Per Cent with Fever*
1899	Freudweiler (*132*)	—	26
1900	Osler and McCrae (*165*)	150	49
1914	Friedenwald (*166*)	472	43
1916	Fenwick (*178*)	—	33
1916	Smithies and Ochsner (*167*)	79	15
1923	Briggs (*134a*)	74	34
1936	Singer and Steigmann (*177*)	1000	35

The following is a case of obscure fever anemia and splenomegaly in which post mortem examination revealed a leio-

myosarcoma of the stomach with perforation into the spleen and into a subdiaphragmatic abscess with extension into the retropentoneal space and destruction of the left adrenal gland

CASE 5 A 32 year-old man had been perfectly well until 6 months before admission when he began to feel run down. Two months later he passed a black formed stool and was admitted to a local hospital where he had a moderately elevated temperature with a persistently enlarged spleen together with anemia Stool examinations revealed no blood Blood cultures agglutinations and x rays failed to reveal the cause of his illness He was given a transfusion just before being discharged home He continued to feel weak and constantly had an elevated temperature splenomegaly and anemia and was admitted to another hospital for 3 weeks undergoing another complete examination He was finally transferred to a larger hospital

The patient had had pneumonia at the age of 3 At the age of 19 he was hospitalized for 5 days with "congestion" of the kidneys The hospital record revealed albumin but no cellular material His best weight was 170 pounds and the admission weight was 146 pounds

The admission temperature was 101 2 the pulse 104 the respirations 26 and the blood pressure 100/52 The spleen descended 2 fingerbreadths below the costal margin and was firm and slightly tender

Laboratory data Two specimens of urine showed a slight trace of albumin The specific gravity ranged from 1 002 to 1 020 The hemoglobin was 58 per cent and the red cell count 3 700 000 The white cell count ranged between 8200 and 13 800 for 3 weeks and then rose slowly to 29 400 Two of nine stools showed a 2+ guaiac reaction A phenol sulfonphthalein test revealed 33 per cent excretion in 30 minutes and 36 per cent in 2 hours A flat plate of the abdomen showed several calcified nodules in the upper left abdomen thought to be located in the kidney or spleen

Course The initial impression was Hodgkin s disease The patient continued to have an elevated temperature with occasional peaks of 104 several times accompanied by a shaking chill After x ray examination showed calcification in the area of the spleen, the diagnosis was changed to tuberculosis

of the spleen However skin tuberculin tests were negative down to a dilution of 1 100 During the third week the patient developed pleural pain in the left shoulder and tenderness in the left upper quadrant The tenderness increased markedly so that he was restricting the motion of the left side of his chest There was a rise in pulse to 120 with a more persistently elevated temperature between 102 and 103

At laparotomy on the twenty eighth day a large subphrenic abscess yielding a variety of organisms on culture including *E coli* staphylococci and hemolytic streptococci was drained One hundred and forty cc of turbid sterile fluid was removed from the left side of the chest The course continued to be stormy with a pulse of 120 and a daily temperature to 101 Five weeks after the first operation a splenectomy was performed The patient s condition became slightly worse with the pulse rising to 140 and the respirations to 40 He was given twelve transfusions but the course was progressively downhill and another exploratory laparotomy was carried out No peritonitis was found but an abscess was found in the left upper quadrant The patient died suddenly

From this brief review it can be concluded that fever is present at some time in the course of cancer of the stomach in 15 to 49 per cent of all gastric malignancies Occasionally it is present before any gastrointestinal symptoms are noted Cases have been reported in which the fever has been low grade continuous remittent or even intermittent with chills It may be the presenting symptom without other signs of tumor Also it may follow perforation pyogenic metastatic infection (of the endocardium spine or joints) or infection of the stomach wall The cases that may be obscure for a long period of time are those that cause fever with or without chills in which there are no other signs of a tumor In all patients with a persistent obscure fever a thorough investigation of the gastrointestinal tract is indicated As has been pointed out the cause of fever in some of these patients is not necessarily a pyogenic complication as was true in the case just presented but may be the tumor itself

LYMPH NODES

In 1889 Voelckers (*179*) described a case with obscure fever which was eventually shown to be sarcoma of the retroperitoneal lymph nodes The patient was a 30 year-old man who had a slowly rising and falling fever Because of the fever the case was considered clinically to be of infectious origin

Lintz (*148*) described the case of a 37 year old man with a retroperitoneal tumor who complained of afternoon fever for 3 or 4 weeks before admission varying from 100 to 103° daily *Six* weeks before admission he developed a dry cough A small node was discovered in the left lower anterior cervical chain and biopsy was performed The pathologic diagnosis was a well-defined large round cell sarcoma completely destroying the normal lymph node architecture The patient died during the eighth week The diagnosis at autopsy was retroperitoneal sarcoma with metastases in the intestine spleen kidney lung mediastinum and cervical nodes

The following case exemplifies the difficulty of diagnosing fever caused by retroperitoneal tumors

CASE 6 A 15 year old boy complained of swelling in the right groin of 4 weeks duration Eight weeks before admission he had abrupt onset of generalized malaise pain in the right groin and continuous fever He lost his appetite and strength became constipated and noted afternoon chilliness followed by sweating He also had intermittent pains between the shoulderblades Four weeks before admission there appeared a swelling in the right groin which increased in size The pain in this region was increased by motion and became more severe In 8 weeks there had been a weight loss of 20 pounds.

Physical examination revealed a few small left anterior cervical nodes There was moderate tachycardia with a systolic blowing murmur present at the apex. The abdominal wall was tense and nontender There was a pea sized nodule in

the left axilla and a small right epitrochlear node There was a lemon sized tender hot fluctuant mass in the inner aspect of the right groin below Poupart s ligament The overlying skin was red tense and peeling There were a few soft enlarged glands in the left groin There was limitation of motion and pain on movement of the knees and hips The temperature was 101 the pulse 106 the respirations 28 and the blood pressure 110/60

Laboratory data The urine showed a trace of albumin Bile was present with absence of urobilinogen during the third week The hemoglobin was 79 per cent The red cell count was 4 200 000 and the white cell count 33 000 with 82 per cent polymorphonuclear leukocytes During the fourth week the hemoglobin fell to 60 per cent The white cell count varied considerably being as high as 82 000 with 55 per cent polymorphonuclear leukocytes and 41 per cent band forms The icteric index was 3 on entry and rose to 90 before death During the third week there was an enlarged hilar shadow on the right side of the chest with prominent markings at the right base

Course The patient was given x ray radiation to the right inguinal region In the first 2 weeks the temperature rose daily to peaks between 101 and 102 Thereafter it was intermittently subnormal and moderately elevated The pulse gradually increased from 90 to 140 and the respirations rose to over 30 The fluctuant mass in the right groin was aspirated on entry and biopsy of a node in the left femoral triangle was later performed The swelling in the right groin abated appreciably on irradiation fluctuation and overlying erythema disappeared and the whole region became markedly indurated The patient constantly complained of severe mid and low back pain in addition to pain in the right shoulder which was acutely aggravated by motion Anorexia pallor weight loss asthenia and drowsiness were progressive During the fourth week the patient developed jaundice and 3 days later went into a deep coma and died

Autopsy revealed an undifferentiated malignant tumor of the lymph nodes mainly retroperitoneal and abdominal There was obstruction of the bile ducts due to compression by lymph nodes accounting for the jaundice in the last few days of the patient s course Tumor cells were found in the fluid of the pleural and peritoneal cavities

HODGKIN'S DISEASE AND LYMPHOMA

The type of Hodgkin s disease that causes obscure fever is localized in the mediastinum or retroperitoneal or mesenteric lymph nodes with or without the simultaneous involvement of the liver spleen, and bone marrow

Messick and Fenner (*180*) reviewed the literature on ab dominal Hodgkin s disease and reported a case with relapsing fever varying between 96 and 104 for 8 to 18 days fol lowed by irregular pyrexia for 3 to 8 days In addition there was anemia and a normal white cell count Eleven months later the spleen became enlarged For the last 3 weeks of the illness there was renal insufficiency and in the last week the patient developed jaundice There was also low blood pressure from involvement of the adrenal cortex Longcope has called attention to the common finding of hypotension in Hodgkin s disease

Fever has also been observed as the presenting symptom in cases of abdominal lymphosarcoma

Foster (*181*) reported 2 cases of obscure fever which were tentatively diagnosed as Hodgkin s disease The patients were treated with x ray radiation became afebrile and were fol lowed for 6 and 15 months respectively without recurrence of fever There was no pathologic confirmation of these cases

Jackson (*182*) reviewed the subject of fever as the main symptom of malignant lymphoma and gave 3 illustrative cases He pointed out that in the Hodgkin s type of malignant lymphoma there is always fever at some time in the course of the disease Other types of lymphoma are apt to show a re mittent or intermittent type of fever when the liver and spleen become involved

CASE 7 A 60 year old man complained of pain in the left axilla which began 3 weeks before admission exaggerated by coughing Physical examination revealed no abnormalities The blood pressure was 118/70 the temperature 99 5 the pulse 90 and the respirations 20

Laboratory data The red cell count on admission was 3 900 000 and the hemoglobin was 60 per cent The white cell count was 14 000 with 81 per cent polymorphonuclear leukocytes 13 per cent lymphocytes 5 per cent monocytes and 1 per cent eosinophils On the sixty fifth day the white cell count was 30 000 On the one hundred forty fourth day it had fallen to 15 000 with a hemoglobin of 50 per cent Many specimens of sputum were examined for tubercle bacilli but none were found

X ray examinations The chest plate on admission was interpreted as consistent with pneumonitis On the fifteenth hospital day the lung fields were within normal limits On the twenty ninth day the left diaphragm was found to be elevated and the possibility of subdiaphragmatic pathology was considered Similar findings were obtained on the forty second day A gastrointestinal series performed on the fifty second day showed ptosis of the stomach On the seventy seventh day hypertrophic arthritis of the dorsal spine was found by x ray On the ninety fifth day the question of subdiaphragmatic pathology was again raised

Course On the seventh hospital day 200 cc of straw colored fluid was removed from the left chest There was temporary subjective improvement but weakness and weight loss continued for over 5 months Two months before death a few cubic centimeters of pus were withdrawn from the right perinephric region A few days before death a mass the size of a tennis ball appeared in the epigastrium and the liver edge became palpable

The patient had a low grade fever for the first 2 months after admission In the third month the fever occasionally rose to 101 This lasted about a month when the temperature was irregularly as high as 104 returning to normal daily The patient became much emaciated and weaker The lungs then started to show signs of edema The heart became irregular The patient died 6 months after the onset of symptoms

Post mortem examination revealed Hodgkin s disease of the mesenteric nodes liver and spleen The spleen was ad

herent to the diaphragm and contained a necrotic area There was also about 500 cc of ascitic fluid

SUMMARY AND CONCLUSIONS

From the foregoing discussion of tumors as a cause of prolonged fever it may be seen that the commonest primary sites are the kidney the liver the bones the lungs and the lymph nodes Certain points stand out when cases of this sort are studied and they are as follows

There is nothing characteristic about the pattern of the temperature in patients with fever associated with tumors The fever may be continuous remittent relapsing or intermittent.

Fever may be a conspicuous feature when the tumor is localized and before metastases occur This is observed in hypernephroma cancer of the lung cancer of the stomach and in hepatoma

Fever is more frequent when tumors have metastasized to the liver or to the bones

When fever recurs some weeks months or years after removal of a primary tumor then metastases to the liver or bone should be suspected also if fever persists after removal of a primary tumor metastases are usually present

CHAPTER IX

Tumors Infrequently Causing Prolonged Fever

In the previous chapter the tumors that frequently cause fever were discussed In this chapter some tumors that may infrequently be associated with fever are discussed

BRAIN

Brodsky *et al* (*183*) recorded a case of brain tumor in a 36 year-old woman who complained of fever of 3 weeks du ration, together with pains in the head and a temperature of 100 to 101° Following the removal of a meningioma the fe ver subsided but the sedimentation rate persisted at high lev els

Marcolongo (*184*) had previously reported a case of cystic frontoparietal glioma with prolonged fever and headache Bouts of unconsciousness and mental stupor pointed to the central nervous system as the source of the fever The author stated that frontal tumors were accompanied by fever in 23 per cent of his cases

Davidson (*185*) reported 5 cases of tumor of the hypothal amus with associated hyperthermia One of the cases was an invasive meningioma of the base of the brain which destroyed the hypothalamus Six years previously this patient had had an

attack of fever and lethargy which was diagnosed as enceph alitis The temperature at that time ranged from 98 to 102° for 3 weeks

Zimmerman (*186*) described a case of brain tumor following fever of a year's duration with dyspepsia anorexia and weakness At autopsy the tumor was found to be small and seemed to involve only the temperature regulating center in the hypothalamus

Friedman (*187*) reported a case of brain tumor in a 62 year old man with a history of change in personality mental deterioration and drowsiness He was disoriented as to time and place The pupils reacted sluggishly to light There was right facial weakness central in type and deviation of the tongue to the right At operation on the thirtieth day an area of softening of the left frontotemporal zone was noted At autopsy a large tumor in the right thalamus and hypothala mus was found which invaded these structures ventrally and medially and extended from the lateral wall of the third ventricle as far down as the tuber cinereum and as high up as the teniae thalami Histologically it was a disseminated neurospongioblastosis

Strauss and Globus (*188*) reported 3 cases of cerebral neoplasm in which fever was a prominent symptom All the patients had lesions in or near the hypothalamic zone

BREAST

Tumors of the breast rarely cause fever except when there are metastases or a lymphangitic spread with signs of acute inflammation That breast tumors may be associated with fe ver without signs of inflammation or metastases has been reported by Johnson (*189*) In any patient with fever then the breasts should be examined for a tumor or if a breast tumor

has been removed in the past and fever appears one should suspect metastases, especially to the liver or bones

Cancer of the breast causes fever when there is a rapidly spreading tumor associated with the signs of acute inflammation (mastitis carcinomatosis) when there are metastases especially to the liver and rarely when the tumor is localized to the breast

In the cases of mastitis carcinomatosis there is an acute inflammation of the breast which extends rapidly beyond its limits and even involves the side of the chest the shoulder and the arm The appearance is that of a diffuse rapidly spreading inflammation rather than a new growth

When metastases occur and produce fever the liver the lungs and pleura or the bones are most often involved

Cancer localized to the breast is likely to produce fever *without* signs of acute inflammation or metastases Such a case was described by Johnson A woman with a lump in the breast had fever for 4½ weeks with no other associated signs of infection A carcinoma was found and removed following which the temperature returned to normal and remained so without recurrence of the tumor

ESOPHAGUS

While cancer of the esophagus is usually seen without fever there have been cases where fever played a prominent role It is not necessarily an index of bacterial infection complicating the carcinoma Liver metastases are frequently present The following is an illustrative case

CASE I A 55 year old man complained of abdominal pain Until the present illness he had consumed half a pint of whisky daily One month before admission severe pain began in the right upper quadrant radiating across the epigastrium and through the back to the right scapula At the

same time there were chills fever and sweats Following this there were intermittent periods of pain not related to eating or activity For at least 9 years the patient had had a cough which was definitely aggravated 2 weeks before admission and became productive of whitish sputum He was admitted with a diagnosis of emphysema and gastritis

On admission the blood pressure was 130/90 The tongue was coated The chest was hyperresonant, with diminished breath sounds at the base of the lungs and prolonged wheezing respirations Both diaphragms seemed elevated The abdomen was held tightly especially in the epigastrium There was dullness in the right upper quadrant extending 4 to 5 fingerbreadths below the costal margin

Laboratory data The hemoglobin ranged from 75 to 80 per cent The red cell count was 4 000 000 The white cell count on admission was 25 000 and continued at this level until the eleventh day when it rose to 68 000 The differential count showed from 87 to 90 per cent polymorphonuclear leukocytes with an average of 30 band forms

Course During the first 2 days the temperature ranged between 99 and 101 It then remained normal until the tenth day when it rose again to 100 The pulse ranged from 80 to 110 and the respirations from 25 to 30 On the fifth day rales were heard at the left lung base posteriorly On the eighth day when preoperative medication was given for laparotomy the liver edge was palpable 4 to 5 fingerbreadths below the costal margin During the postoperative course there was intermittent slight tenderness in the right upper quadrant. Postoperatively the pulse temperature and respiratory rate rose rales developed at both lung bases and the patient died on the sixteenth day

The diagnosis at autopsy was carcinoma of the esophagus

JEJUNUM

Cancer of the jejunum is a rare entity A further reason that study of the small bowel should be included in a patient with prolonged fever is illustrated by the following case

CASE 2 A 45 year-old man complained of weakness and fever of 11 months duration Eleven months before entry there was onset of severe night sweats Two months later the

patient was hospitalized for 7 weeks He was given two blood transfusions and was discharged home on liver and iron He continued to lose strength and had a nightly fever of 99 to 100 For 5 months prior to admission the patient had extreme fatigue and severe anorexia For 3 months he had occasional nocturia and noted tingling of the feet and tenderness of the toes on pressure He had lost 25 pounds On admission there was an area of hyperesthesia over both feet from the mid dorsum to the tips of the toes

Laboratory data The hemoglobin was 16 per cent the red cell count 1 960 000 and the white cell count 11 000 with 57 per cent polymorphonuclear leukocytes 9 per cent band forms 1 per cent eosinophils 21 per cent lymphocytes, and 12 per cent monocytes There were 613 000 platelets and 2 1 per cent reticulocytes The hematocrit was 20 per cent. The total serum protein was 6 2 Gm per 100 cc with 3 39 Gm of albumin and 2 81 Gm of globulin The blood sedimentation rate was 150 mm per hour Five blood cultures were negative

Course The pulse varied between 100 and 130 The daily temperature rose to 103 or 104 each night for 10 days and to 100 for 4 days The patient was given seven transfusions after which the hemoglobin was 55 per cent and the red cell count 3 540 000 He received deep x ray therapy totaling 1125 r to the upper abdomen without effect The marked weakness persisted An exploratory laparotomy was attempted but the blood pressure fell to an imperceptible level and the operation was discontinued The patient was discharged home and expired in 4 months

Autopsy examination limited to the abdomen revealed an annular and circulating tumor 2 cm in width 75 cm from the ligament of Treitz The lymph nodes in the immediate vicinity were enlarged with some necrotic nodules present. The lumen of the bowel was encircled and the serosa was intact. The tumor had a necrotic center The pathologic diagnosis was annular carcinoma of the jejunum cell type undetermined

PANCREAS

In 1876 Janicke (*190*) mentioned a case of carcinoma of the pancreas with icterus fever and chills as the major symp-

toms In 1892 Kobler (*131*) reported the case of a patient with the same condition in whom hectic fever was the pre dominant symptom Terminally this patient developed peritoni tis

CASE 3 A 53 year old man complained of breathlessness and of pain in the right side on deep breathing Three weeks before admission he had onset of pain that restricted breath ing while lying on his right side or bending The pain was located in the right upper quadrant just below the costal margin Physical examination revealed only an enlarged tender liver compressing the base of the right lung

Course The patient had an irregular temperature between 99 and 103 The white cell count rose to between 12 000 and 25 120 with 75 per cent polymorphonuclear leuko-cytes On one occasion a friction rub was heard over the liver Late in the course of the illness the patient developed obstructive jaundice and died

Autopsy examination revealed carcinoma of the tail of the pancreas with metastases to the retroperitoneal lymph glands liver peritoneum pleura and lungs There were also thrombi in the pelvic veins with multiple pulmonary emboli and terminal pulmonary edema

COLON

Fever plays an important part in the clinical picture of cancer of the colon as is shown in the following case reports

CASE 4 A 31 year old woman complained of pain in the left side which began 19 months before admission follow ing delivery of her fourth child and became progressively worse She had had night sweats and had lost 24 pounds in weight Her physician found a mass in the left upper quad rant which was thought to be an enlarged spleen Three months before admission she had several chills One shak ing chill was followed by extreme orthopnea great difficulty in expiration pounding of the heart with dull precordial pain and throbbing in the ears Blood culture yielded non hemolytic streptococci

On physical examination the apex impulse of the heart could not be clearly identified The first sound at the apex

was roughened and was followed by a harsh systolic murmur transmitted to the axilla and up to the precordium There was a firm mass in the left hypochondrium extending 8 cm below the costal margin in the left mid clavicular line The edge was firm. A notch could be felt on its medial border This mass was slightly tender and moved on respiration.

Course The temperature ranged from 98 to 101 5 The hemoglobin was 47 per cent and the red cell count 3 400 000 The white cell count was 11 250 An upper gastrointestinal series revealed that the stomach was pushed to the right by the mass without evidence of erosion Throughout the course of her illness the patient had diarrhea but no melena

At operation a carcinoma of the colon with metastases was found A transverse colostomy was performed Death occurred on the twenty sixth hospital day Autopsy revealed carcinoma of the transverse colon with metastases to the regional lymph nodes and involvement of the duodenum with the formation of communications at two points between the lumen of the transverse colon and duodenum

CASE 5 A 65 year old man complained of generalized wasting of 15 months duration with loss of strength and indigestion characterized by sharp stabbing epigastric pains coming on 15 to 20 minutes after meals and lasting 30 to 40 minutes There was no diarrhea but some constipation There had been an undeterminable loss of weight For 3 months the tongue and mouth had been sore There were occasional severe vomiting spells

The positive physical findings included pain and tenderness in the left upper quadrant rales at the left lung base posteriorly and tachycardia

Laboratory data The red cell count was 3 672 000 and the hemoglobin 28 per cent The white cell count was 14 000 on admission and thereafter ranged from 8000 to 17 550 Gastric analysis revealed 16 units of free hydrochloric acid and 27 units of combined acid The stools showed a 4+ guaiac reaction

Course The patient had a persistent low grade fever to 100 His course was one of gradual deterioration ending in death The diagnoses at autopsy were carcinoma of the splenic flexure of the colon with metastases to the liver lung, and mesenteric and retroperitoneal lymph nodes and hemorrhagic colitis

RECTUM

Obscure fever has been reported in carcinomas of the rectum which have been overlooked Karsner (*191*) reported the case of a 10 year old girl with carcinoma of the rectum who was thought clinically to have tuberculous peritonitis Briggs (*13-b*) reported fever in 36 9 per cent of uncomplicated tumors of the colon and rectum

This case of carcinoma of the rectum was followed as a case of prolonged fever

CASE 6 A 20 year-old man complained of pain in the abdomen and fever Seven months before admission he had a sudden attack of severe abdominal pain in the left lower quadrant associated with dysuria frequency and retention of urine for 24 hours There was some burning on urination and a little fever There was constipation but no diarrhea The patient recovered in 15 days but 5 months later he was again seized with pain in the left lower quadrant Thereafter he had loss of appetite loss of weight night sweats and colicky pain associated with defecation or the passage of gas There was blood and mucus in the stools tenesmus frequency of urination frequency of desire to urinate and terminal hematuria The patient thought that he felt a lump which rose in the abdomen in association with the pain and disappeared with the passage of flatus or feces The stools had been pencil like

Physical examination showed the head and chest to be normal except for marked acne vulgaris There was tenderness in the left lower quadrant A tumor mass was felt by rectal examination

Laboratory data The white-cell count was 12 000 to 13 000 A barium enema was negative The stools showed blood and mucus

Course The patient had a spiking fever ranging from normal to between 101 and 103 A diagnosis of adenocarcinoma of the rectum was made at the time of surgery

CHAPTER X

Blood Dyscrasias

Fever is a common occurrence during the course of many of the diseases of the blood forming organs In most cases this feature is well recognized as part of a progressive illness together with the other features characteristic of the disease In other cases fever may be the only and main symptom of the disorder for many weeks or several months before other symptoms or signs appear The fever may be continuous remittent or relapsing The diseases which may at first be present with fever as the main symptom are discussed in this chapter

The examinations which are most important are a careful study of the peripheral blood x rays of the bones, and bone marrow biopsy or sternal marrow puncture Very often the diagnosis can be made only after following the course of the illness

The most confusing cases are those with fever and a normal or reduced total white cell count with no abnormal leukocytes appearing in the peripheral blood smear Repeated blood cultures should be carried out early in these cases in order to rule out an overwhelming bacteremia

AGRANULOCYTOSIS

When fever appears in this disease there is always a neutropenia and leukopenia generally accompanied by signs of an

acute infection in the nasopharynx or elsewhere Commonly there is a history of ingestion of drugs such as aminopyrine dinitrophenol or other agents Otherwise there may be a history of exposure to other poisons such as benzol The hemoglobin red cell count and platelet count are normal

Rutledge *et al* (*193*) recorded a remarkable instance of cyclic agranulocytic angina associated with recurrent fever and constitutional signs in a man 20 years of age The onset of irregular remittent fever was at 2½ years of age with recurrent attacks of furunculosis

Several interesting reports were subsequently added to the literature showing an association of agranulocytosis with the menstrual cycles Thompson (*194*) reviewed 40 cases of agranulocytosis at the Presbyterian Hospital in New York Of the 35 women in his series 25 were within the menstrual age In 3 of these cases the history was incomplete in 2 cases there had been artificial menopause and in 2 cases neutropenia appeared with endometritis following abortion The other 18 women were menstruating at the time of admission In 17 of these cases the onset of symptoms occurred within 1 or 2 days of the regular menstrual period One or more recurrences were observed in 6 patients coincident with catamenia

Thompson reported further on the case of a man reported by Rutledge *et al* (*193*) Since the previous observations attacks had occurred every 3 weeks In the preceding 2 years the patient had developed a true diabetes insipidus which had responded to posterior pituitary extract Pentnucleotide had partially controlled the leukopenia Endocrine studies had revealed that the patient excreted enormous amounts of female sex hormone which fluctuated in the same manner as in a normally menstruating woman

Jackson and Merrill (*195*) reported the case of a 30 year

old woman who had had four attacks of agranulocytic angina in the 2 years preceding the first examination All relapses were initiated precisely on the first day of the menstrual period At no time until 10 months after first seen was she acutely ill Pentnucleotide gave hematologic and clinical improvement Four months later she developed a severe infection and expired Doan (*196*) pointed out that the relationship to menstruation is not a constant one but that 80 per cent of the cases of agranulocytosis occurred in females

Jackson and Parker (*197*) stated that in agranulocytosis the fever had nothing characteristic about it As a general rule the temperature reaches a maximum of 103 or 104° Rarely it may rise to 106 or even 107° In some patients only a moderate hyperpyrexia is the rule A steady, high unremitting temperature is of extremely grave prognostic import.

Reimann and deBardinis (*41*) collected 16 cases of periodic (cyclic) neutropenia from the literature or their own experience Most of the patients menstruated every 3 weeks Fever was attributed to infection The antihistaminic drugs had no effect on the cycles

ALEUKEMIC LEUKEMIA

Alt and Barker (*1*) reported 2 cases followed after discharge from the hospital and diagnosed as *lymphoblastomas* One of these was an aleukemic leukemia That a sternal marrow study was performed in this case is doubtful since this diagnostic aid was rarely employed at that time Mallory (*198*) reported the following interesting case

CASE I A 38 year-old man was admitted with the chief complaint of sweating and fever Five weeks previously he had a severe shaking chill followed by fever and profuse sweating On 3 subsequent days he had chills but thereafter

none Up to 2 weeks before entry he had a gradually rising fever in the morning which subsided toward evening together with profuse night sweats and progressive weakness The fever rhythm then changed and the patient had an evening fever of 104 and 105 and a morning temperature of about 96 He lost weight developed anorexia and became slightly weaker There had been some frontal headache moderate polydipsia and a slight cough productive of a small amount of mucoid material without any associated symptoms He had been given a course of quinine therapy without effect. On several occasions just before entry macroscopic hematuria was noted

At physical examination the skin was hot and dry The eyes were slightly prominent The right eyelid was puffy and the right pupil was slightly irregular The tongue was heavily coated and the breath had a foul odor The oral hygiene was poor There was slight dullness at the right lung base posteriorly with slightly diminished tactile fremitus and breath sounds The abdomen was slightly distended and tympanic There was moderate edema of the ankles and some coarse tremor of the extremities The temperature was 104 4 the pulse 110 the respirations 20 and the blood pressure 106/58

Laboratory data The urine was normal The red cell count was 3 600 000 and the hemoglobin 70 per cent The white cell count was 7400 with 68 per cent polymorphonuclear leukocytes 22 per cent lymphocytes 3 per cent monocytes 6 per cent myelocytes and 1 per cent nucleated red cells The sputum was mucopurulent in appearance and on one occasion contained blood The serum protein was 4 Gm The blood chlorides were 100 and the icteric index was 3

Course The temperature remained between 102 and 104 but the white cell count did not rise above 9000 The patient gradually developed increasing edema as the serum protein fell to 3 2 Gm Signs of fluid appeared at both lung bases and in the abdomen On the ninth day 60 cc of cloudy yellowish fluid was removed from the abdomen The fluid had a specific gravity of 1 010 with a cell count of 60 mostly lymphocytes On the following day 50 cc of straw colored fluid was removed from the left chest The fluid had a specific gravity of 1 006 and formed a pellicle Thirty six white cells were present practically all of them being lymphocytes On the thirteenth day the patient became weaker and irrational with a rise in the respiratory rate The left

pupil became pinpoint and failed to react to light The right fundus showed blurring of the nasal side of the disks and a few fresh hemorrhages A lumbar puncture test showed an initial pressure of 230 with normal dynamics The spinal fluid cell count showed 6 polymorphonuclear leukocytes and 4 lymphocytes Alcohol and ammonium sulfate tests were positive The patient became rapidly worse and expired the following morning

The diagnoses at autopsy were aleukemic myeloid leukemia with involvement of the liver and spleen hydrothorax hydropericardium ascites peripheral edema pulmonary edema bilaterally infarct of the spleen and cholelithiasis

APLASTIC ANEMIA

When aplastic anemia has developed to its fullest state there is usually little difficulty in making the diagnosis However early in the course fever with leukopenia and neutropenia without changes in the other elements of the blood may be the only features of the illness for some weeks Sooner or later a decrease in the other blood elements appears and the diagnosis becomes clear

The following describes the course of a proved case of aplastic anemia

CASE 2 A 58 year-old woman complained of easy fatigue associated with easy bruising of 6 weeks duration Three months previously she had noted bruising on slight trauma or pressure Her hands became cold and she began to tire quickly She was told that she was anemic and was given liver orally Shortly after this she began to bleed from the rectum and from the nose

Physical examination showed a recent loss in weight The skin was dry rough and warm There were a few old bruises present about the hips and thighs There were numerous red spots over the same area and in the mouth Retinal hemorrhages were in evidence particularly on the left There was a thrombosed hemorrhoid with ecchymosis of the right buttock. The heart rate was rapid There was a soft precordial

systolic murmur Examination of the abdomen revealed a palpable nontender liver with its edge just below the costal margin The spleen was not palpable The reflexes were hyperactive throughout The blood pressure was 146/82 and the rectal temperature 101 4

Laboratory data The hemoglobin on admission was 33 per cent with a red cell count of 1 620 000 and a hematocrit of 16 per cent The reticulocytes were 0 4 per cent The blood platelets numbered 32 000 The clotting time was 6 minutes and the bleeding time 25 minutes plus The prothrombin time was 99 per cent of normal The white cell count was 2400 with 12 per cent polymorphonuclear leukocytes 81 per cent lymphocytes and 7 per cent monocytes The total serum protein was 6 71 Gm per 100 cc The icteric index was 13 A fragility test showed hemolysis beginning at 0 42 per cent and complete at 0 20 per cent The stools showed a 4+ guaiac reaction in two out of three specimens The corrected sedimentation rate was 1 mm per minute

Course The patient had a swinging temperature ranging from 100 to 105 She had a frank chill on the fifth day Blood cultures taken at this time showed only *B subtilis* Because of the marked anemia she was given eight transfusions of citrated blood but the hemoglobin on the day before death was 46 per cent The red cell count was 2 220 000 the blood platelets 38 000 and the white cell count 950 Despite all attempts at supportive therapy the patient became gradually worse lapsed into coma and expired on the twelfth day with terminal hemorrhages from all body orifices

INFECTIOUS MONONUCLEOSIS

A case recorded by Rinzler and Hertz (*199*) is a good example of an unusual temperature curve in a case which was not diagnosed as infectious mononucleosis until the fifteenth day of the illness

CASE 3 A 25 year old man was admitted with malaise fever and swelling of the glands in the left side of the neck of 6 days duration

Physical examination revealed a temperature of 101 and

enlargement of the left posterior cervical chain Later there was involvement of the right posterior cervical glands and right occipital nodes During the third week of illness the patient had a violent chill followed by temperature elevations between 101 and 104 8 accompanied by profuse sweating The temperature returned to normal within 3 hours The chill was always preceded by an ache in the lower back which increased as the temperature rose

The white cell count on the eleventh day of illness was 7950 with 53 per cent polymorphonuclear leukocytes (38 per cent segmented) 40 per cent lymphocytes and 7 per cent monocytes On the fifteenth day heterophil agglutination was positive in 1 64 dilution the white cell count was 14 700 and there were 18 per cent abnormal lymphocytes characteristic of infectious mononucleosis The patient had an uneventful recovery

Worthington and Fleischaker (*200*) reported another perplexing problem of fever

CASE 4 A 20-year old man was operated on for a right inguinal hernia and developed a hematoma at the operative site In the evening of the fourth postoperative day the temperature reached 104 2 A few small lymph nodes in the left side of the neck and in the axilla were noted The white cell count was 4800 with 65 per cent polymorphonuclear segment forms 4 per cent band forms and 31 per cent lymphocytes The patient was already receiving penicillin and sulfadiazine

During the next 4 days the temperature rose rapidly from 100 to 104 On the seventh postoperative day the smear revealed one third of the lymphocytes to be large and abundant occasionally with vacuolated cytoplasm Three days later a generalized maculopapular eruption appeared on the face neck arms body and legs On the following day the patient s condition was very serious and he was given a transfusion The red cell count had fallen to 3 460 000 Many agglutinations were carried out and were normal The patient s condition gradually improved and he became ambulatory 21 days after operation Six weeks after operation the heterophil agglutination was still positive in a dilution of 1 224

OSSFOUS MYELOID DYSPLASIA

This disease was described by Grulee *et al* (*192*) in a 7-year-old boy The main features of the condition were a high irregular fever which persisted for 3 or 4 months marked leukopenia progressive thinning of the cortex of all the bones and alteration in the bone marrow which did not conform to multiple myeloma The diagnosis was made by x ray examination of the bones and histologic examination of the bone marrow

PLASMOSARCOMA

Fever was the chief complaint in the following case which was proved by biopsy of the gums to be plasmosarcoma an extremely rare disease

CASE 5 A 13 year old boy complained of fever reaching 101 for 3 weeks At the onset of the illness there was a slight aching in the right calf Two weeks before entry he developed a slight painless swelling of the right cheek associated with difficulty in opening his mouth

At physical examination the eardrums showed retraction and reddening most marked on the left side There was nasal crusting and purulent discharge in the right nostril The tongue was heavily coated There were small palpable glands in the neck under the jaw The right cheek was swollen The heart was moderately enlarged with a slightly rough blowing systolic murmur at the apex. P_2 was louder than A_2 The blood pressure was 110/65 the temperature *100 8* the pulse 120 and the respirations 22 The weight on entry was 71 pounds (normal 85 to 90)

Laboratory data The urine had a specific gravity between 1 011 and 1 022 with a very slight trace of albumin on one occasion The hemoglobin on admission was 96 per cent with a red cell count of 5 700 000 At discharge it was 78 per cent The white cell count was 16 100 with 82 per cent polymorphonuclear leukocytes 17 per cent lymphocytes and 1 per cent monocytes It fell to 10 200 the day after admis-

sion and then rose to between 13 900 and 29 400 On dis charge it was 14 800 The sputum was negative for tubercle bacilli The sedimentation rate was 1 2 *mm* per minute A chest x ray on admission showed enlarged hilar glands On the eleventh hospital day the antra showed evidence of dense infection by x ray Six days later multiple areas of destruction were seen in the skull ribs and scapulae suggesting either disseminated osteomyelitis lymphoma or osteitis fibrosa cys tica

Course During the hospital stay several polypoid masses 1 to 2 cm in diameter grew from the alveolar margins of the gums at various points At the end of the third week the temperature still varied between 100 and 102 A biopsy of the gingiva revealed a plasmosarcoma Death occurred in the fourth week.

CHAPTER XI

Noninfectious and Non neoplastic Diseases

In this chapter we have listed and collected some of the in frequent causes of prolonged fever not due to either an in fection tumor or blood dyscrasia They include a variety of conditions in which the cause is unclear but for purposes of future investigation and study they should be included with other diseases in which fever may be prolonged

AMYLOID DISEASE

An interesting case was reported in the Cabot Case Records (*201*) of the Massachusetts General Hospital

CASE 1 A 46 year old man was admitted complaining of intermittent fever Four months before admission he devel oped bronchopneumonia and was ill for 3 weeks with a tem perature up to 102 moderate cough without bloody sputum and slight diarrhea He received sulfadiazine for 1 week with out benefit and then penicillin with slow improvement He became asymptomatic during the next few weeks but was unable to regain the 25 pounds in weight which he had lost. He had definite atrophy of the muscles of the arms and shoulders Two and a half months prior to admission he noted listlessness easy fatigability and an afternoon tempera ture to 100 5 followed by profuse sweating Febrile rises oc curred periodically

The patient had had nocturia twice nightly for many years

He frequently had nausea vomiting and chest pain For 5 years he had had attacks of migratory arthralgia relieved by aspirin On several occasions he had a periarticular swelling of the hands and knees suggesting urticaria

The temperature on admission was 99 the pulse 100 the respirations 20 and the blood pressure 132/82

Laboratory data The white cell count was 8600 with 73 per cent neutrophils 22 per cent lymphocytes 1 per cent mononuclear cells and 4 per cent eosinophils The hemoglobin was 11 8 Gm The specific gravity of the urine ranged from 1 002 to 1 006 with albumin 3 to 4+ The urinary sediment showed only occasional red cells white cells and casts The blood sedimentation rate was 13 mm per hour The nonprotein nitrogen was 18 mg per 100 cc the calcium 8 8 mg and the phosphorus 3 3 mg The alkaline phosphatase was 3 7 units A cephalin flocculation was 2+ in 48 hours The total protein was 6 95 Gm with an albumin globulin ratio of 1 1 8 Tuberculin (O T) was positive in a dilution of 1 100 in 24 hours

A film of the left knee showed slight hypertrophic changes about the articular surfaces consistent with a slight degree of osteoarthritis On a Graham test the gallbladder filled with well concentrated dye and contained a rounded nonopaque shadow consistent with calculus A gastrointestinal series demonstrated a constant narrowing in the prepyloric region for a distance of 3 cm In the center of the narrowed portion a constant collection of barium measuring 1 cm in diameter was seen A plain film of the abdomen demonstrated that the right renal shadow was larger than the left

The hospital course was essentially afebrile and the patient was discharged home after a week A gastrointestinal series 1 month later at another hospital suggested a duodenal ulcer with antral spasm Following discharge the patient had persistent fever and fleeting severe joint pains progressive weight loss bloody diarrhea persistent vomiting and oliguria Joint pains and fever continued until death 1 month after discharge

Autopsy examination revealed an enlarged liver and spleen and greatly enlarged kidneys The gross appearance was so characteristic of amyloid disease that an iodine reaction test was carried out confirming the diagnosis A healed benign peptic ulcer was demonstrated close to the pylorus Microscopic sections of bone marrow revealed replacement by im

mature cells faintly res mbling plasma cells but within the limits of what is seen in certain cases of multiple myeloma In the kidneys there was severe hyaline degeneration in the convoluted tubules

ALLERGIC FEVER

Janeway and Mosenthal (*202*) recorded the case of a 16 year-old girl who had recurrent attacks of fever prostration abdominal pain tachycardia and leukocytosis The past history revealed only measles and diphtheria

CASE 2 Onset of attacks which at first came monthly with the longest interval 10 weeks was at the age of 2 weeks For a year before she was seen the attacks occurred weekly She was observed for two 4 week periods in a 6 month period with a careful temperature record of the in tervening period In the 6 months there were fourteen at ta ks five severe and nine mild

The prodromal stage of the attack was uneasiness loss of appetite and epigastric and abdominal discomfort lasting for 4 to 12 hours Generally the symptoms increased into what was described as the crescendo phase characterized by pros tration increased abdominal pain fever tachycardia and poly morphonuclear leukocytosis The pain was chiefly abdominal and colicky Occasionally it was referred to one or the other shoulder to the hip or even to the feet Occasionally head ache was present Physical examination revealed abdominal ri gidity and tenderness usually on the side of the umbilicus The maximum temperature was 104 the pulse rate 140 and the white cell count 28 800 There was complete anorexia and marked salivation In severe attacks there was nausea and retching with vomiting once or twice at the height of the attack The vomitus consisted of the contents of the pre vious meal together with mucus and free hydrochloric acid The duration of the crescendo period was 8 to 16 hours

In the third phase there was a rapid subsidence of all symptoms The pain stopped first followed by the fever then the tachycardia and finally the leukocytosis Within 12 hours the patient had a voracious appetite

He frequently had nausea vomiting and chest pain For 5 years he had had attacks of migratory arthralgia relieved by aspirin On several occasions he had a periarticular swelling of the hands and knees suggesting urticaria

The temperature on admission was 99 the pulse 100 the respirations 20 and the blood pressure 132/82

Laboratory data The white cell count was 8600 with 73 per cent neutrophils 22 per cent lymphocytes 1 per cent mononuclear cells and 4 per cent eosinophils The hemoglobin was 11 8 Gm The specific gravity of the urine ranged from 1 002 to 1 006 with albumin 3 to 4+ The urinary sediment showed only occasional red cells white cells and casts The blood sedimentation rate was 13 mm per hour The nonprotein nitrogen was 18 mg per 100 cc the calcium 8 8 mg and the phosphorus 3 3 mg The alkaline phosphatase was 3 7 units A cephalin flocculation was 2+ in 48 hours The total protein was 6 95 Gm with an albumin globulin ratio of 1 1 8 Tuberculin (O T) was positive in a dilution of 1 100 in 24 hours

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onstrated in dogs that stopping of the heart or compression of the thoracic aorta was followed by a rise in the temperature of the liver and intestinal contents Cessation of respiration on the other hand, was followed by a fall in temperature

In 1873 Ackerman showed in dogs that while internal tem perature rose, peripheral temperature fell when the heart stopped and respirations were continued by artificial means

Steele (*209*) found that the surface temperature of cardiac patients was lower than that of normal individuals whereas patients with infectious fever had normal or elevated surface temperatures He concluded that elevation of rectal temperature in cases of heart failure need not be of infectious origin but might depend on a variety of processes incident to the heart failure itself

Septal Infarction An unusual cause of obscure fever is septal infarction of the heart Laubry and Soulie (*210*) reported the case of a man 44 years old who had fever for 9 months He first came under observation with complete heart block, a rate of 44 dyspnea and palpitation Fever varied from 102 6 to 104 0 There were one or two remissions of about 15 days duration The heart became accelerated during this period Blood cultures were negative and there were no other signs of infection. Autopsy showed infarction of the heart with extensive involve ment of the septum There was no pain at any time These authors failed to reach any definite conclusions as to the cause of the fever

DIFFUSE COLLAGEN DISEASE

Klemperer *et al* (*211*) employed the term diffuse colla- gen disease to indicate that in disseminated lupus erythemato- sus and in diffuse scleroderma the basic morphologic changes

tive heart failure with 153 showing an elevation of rectal temperature above 100° on two or more occasions In 49 of these cases there was no recognized explanation of the fever The authors reported in detail 5 cases of varying cardiac etiology in which fever appeared and gradually increased with increase in tachycardia dyspnea and gain in weight before dullness at the lung bases or jaundice became discernible When digitalis was given and recovery started the temperature returned to normal The authors pointed out that when digitalis is given for acute rheumatic fever or pneumonia there is no change in the temperature pattern Instances where the relation of fever to heart failure stands out most clearly are those of attacks of paroxysmal tachycardia In some of the cases cited it was possible by observing the body weight to distinguish between fever due to an infectious process and that due to congestive heart failure In fever from heart disease there is a gain in weight while if the fever is due to an infectious process there is a slow loss Lung aspirations were made in 34 patients 30 of them with fever, and thirty six of forty puncture cultures failed to grow out any bacteria responsible for the fever Two of the four positive cultures were *B subtilis* one was *Str viridans* and the fourth was *Bacteroides acuminatus* a terminal invader which was also found at post mortem examination on the following day

Thacher (*206*) raised the question whether simple passive congestion of the viscera could produce fever He reviewed 901 cases of chronic endocarditis *505* of which exhibited fever, the cause of which was obscure in 291 cases

Another observation of interest in regard to circulatory failure as a cause of fever was made by Wunderlich (*9*) in 1871 It confirmed the work of Seume (*207*) indicating that following death when the circulation has ceased the temperature of the body sometimes continues to rise Further experimental work in this regard was done in 1870 by Heidenhain (*208*) who dem

with peaks of fever as high as 101 The blood pressure was never above 120/80 The patient was treated with salicylates iron, a high vitamin diet physiotherapy and intravenous typhoid vaccine Subcutaneous nodules were noted on several occasions especially after temporary discontinuance of the typhoid therapy The patient was greatly improved on discharge 11 weeks after entry The diagnosis was chronic rheumatoid arthritis

Two days after discharge the patient had the return of painful joints and nodules The joints involved were those of the feet ankles knees hips wrist elbows and hands There was no improvement on a regime of 90 grains of aspirin in addition to codeine daily Three weeks after discharge therefore the patient was admitted to the Boston City Hospital Additional history obtained at this time included the occurrence of malaria in childhood and admission to another hospital 3 years before with epistaxis and anemia The patient had had frequent headaches and occasional colds

The admission blood pressure was 120/90 the temperature 99 8 the pulse rate 102 and the respirations 28 The throat was injected There were small postaural cervical and inguinal glands The heart was considered borderline in size and was 8 5 cm to the left of the mid sternal line There was a faint poorly transmitted apical systolic murmur There was moderate swelling of both ankles and knees with limitation of motion of the ankles and wrists most marked on the right All joints were tender and there was moderate wasting and atrophy of the leg muscles Over all the extremities there were bean sized tender subcutaneous nodules

Laboratory data The urine was negative except for occasional white cells up to 30 in number In one specimen there were also occasional red cells and rare granular casts The hemoglobin ranged from 64 to 77 per cent The red cell count was 4 470 000 The white cell count was 8800 The Kahn test was negative The nonprotein nitrogen was 40 mg per 100 cc. on admission and later was 26 mg The phenol sulfonphthalein excretion was 90 per cent of normal The sedimentation rate was 1 45 mm per minute Aerobic and anaerobic cultures were negative Electrocardiograms showed a high P_1 and slight left ventricular predominance

The patient was given salicylates orally and wintergreen liniment was applied locally on the affected joints Initially

Fever Due to Intercurrent Infections in Cirrhosis of the Liver The infections that may occur during the course of cirrhosis of the liver causing fever that is difficult to interpret, are chronic pyelonephritis bacterial endocarditis with negative blood cultures and without murmurs and chronic cholangitis

In some patients with latent cirrhosis of the liver who develop an intercurrent infection all the signs of active liver necrosis may follow The liver and spleen enlarge jaundice appears and attention may be centered on the liver rather than on the primary infection

Also patients with liver disease may have recurrent attacks of abdominal pain with an increase in jaundice simulating cholelithiasis At operation no stones are found These are cases of so-called *Pseudogallenstein* colic of the German school Their cause is obscure They are seen in sickle cell anemia as well as in other disorders

DRUG HYPERSENSITIVITY

Drugs seldom cause fever so that those frequently used are usually not suspected If there is a rash accompanying the fever the drug is more likely to be suspected Some of the drugs which are known to cause obscure fever include the barbiturates sulfonamides arsenicals and iodines

Iodism Barker and Wood (*213*) have emphasized that the administration of iodides may result in fever In a review of 400 cases of hyperthyroidism treated with iodine they found 7 cases (1 75 per cent) with severe febrile episodes as a direct result of this medication Some of their patients also had cutaneous eruptions coryza pharyngitis enlargement of the lymph nodes and eosinophilia as accompanying manifestations of toxicity In

1 case jaundice occurred In 1 patient with fever the medication was discontinued and then reinstituted after the eosinophilia had disappeared There was no recurrence of drug fever until almost 2 years later The fever in 4 cases began within 4 days of starting the drug In 3 cases the temperature returned to normal within several days after the iodine had been discontinued whereas in 4 cases the fever persisted for 10 to 30 days after withdrawal In 1 case fever was the only manifestation of drug toxicity

Katzenstein (*214*) reported 2 cases of fever following iodides He referred to a case of spinal meningitis reported by Stengel in which the temperature varied from 98 8 to 100 5 during the administration of iodides The fever quickly terminated when the iodides were withdrawn and reappeared when they were reinstituted Five similar cases were reported by Becherucci (*215*) In only 1 of these however did the fever reach 100 4°

The first case reported by Katzenstein was that of a 62 year-old man who was admitted for hernia The patient was jaundiced and a diagnosis of syphilis of the liver was made Except for the last 2 weeks of hospitalization there was a constant relation between the administration of iodides and the occurrence of fever

The second case was that of a 42 year-old woman with a complaint of severe stabbing pains in the neck for 5 weeks A diagnosis of syphilis of the central nervous system was made Again there was a correlation between the occurrence of fever and the ingestion of potassium iodide To these two cases of fever as the sole manifestation of iodism are added the following two cases

Fever and nodular skin eruption occurred in a woman with chronic bronchitis who received iodine for symptomatic relief of cough Recovery followed the withdrawal of iodides A 67-

Names which have been used in the past to distinguish this illness are zinc fume fever brass founder s ague smelter s shakes zinc chills brass chills metal ague galvanic poisoning and syndrome of Monday night chill and fever

Quinn referred to a group of papers by Drinker Thomson, Sturgis and Finn who studied the effect of experimental inhalation of zinc oxide by normal persons When the material was inhaled on 2 successive days resistance developed These authors thought that the same general reaction might be caused by iron nickel or aluminum

It is therefore important to go into detail in taking the occupational history of any patient who has recurrent chills and chest pain with reasonably good health between attacks

RELAPSING FEBRILE NODULAR NONSUPPURATIVE PANNICULITIS

This condition was first described in 1921 by Christian (*221*) In 1925 Weber (*222*) reported a similar case The condition is characterized by fever in recurring attacks or relapses together with inflammation of the panniculus adiposus nodular in distribution and nonsuppurative Later there is a depression in the contour of the skin which gives a marked appearance of scarring In Christian s case leukocytosis did not accompany the febrile episodes

If panniculitis is overlooked the case becomes a problem of obscure fever when there are no depressed areas in the skin as monuments of previous attacks

BENIGN PAROXYSMAL PERITONITIS

A condition which is most often found in the second and third decades of life as a cause of obscure fever is benign

paroxysmal peritonitis According to Siegal (*223*) it is characterized by recurrent paroxysms of severe abdominal pain with fever which may be as high as 105 Chilliness or shaking chills may accompany the attacks Peritoneal irritation is indicated by subjective abdominal soreness and the objective finding of widespread exquisite direct and rebound tenderness Occasionally true involuntary spasm of the abdominal wall is noted At some stage chest pain of a pleuritic type is present Malaise severe prostration intense nausea and vomiting are almost constant findings An occasional case may show urticarial wheals during the acute episode The etiology of the condition remains unknown The patients often have a family history of food allergy Leukocytosis is frequently present In many cases the diagnosis is made only after a normal appendix has been removed or some other surgical condition has been explored

Reimann (*224*) who has been interested in the subject of obscure fever for many years reported 6 cases of regular periodic disease 3 of which were characterized by fever and abdominal pain The first case which he found in the literature was that of Janeway and Mosenthal (*202*) who reported a 16-year old Jewish girl whose recurrent attacks of fever and abdominal pain started in early infancy at first occurring monthly and later every 7 days The attacks were of varied intensity The temperature was as high as 104 with a white cell count as high as 28 000 The discomfort lasted for 8 to 12 hours and was followed by polymorphonuclear leukopenia, about 30 to 36 per cent No eosinophilia was reported Cooke (*225*) reporting on the same patient stated that attacks were stopped by withdrawing milk from the diet.

One of Alt and Barker s cases (*1*) was that of an 18 year-old boy who at the age of 4 had attacks of pain in the abdomen right arm shoulder and chest vomiting transient splenomegaly fever and leukocytosis every 2 months By the age of 18

the attacks were occurring almost weekly Splenectomy had no effect

Scott and Kirschner (*38*) described a man who at the age of 27 had frequent attacks of itching and urticaria followed by chill malaise temperature to 105° leukocytosis and sometimes arthralgia The last symptom was still present after 14 years Edema of the heat regulating center of the brain was suspected Various foreign protein injections and transfusions had no effect

Allen (*39*) and Wolf and Wolff (*34*) reported the case of a 43 year old man who when last seen had attacks of fever, leukocytosis and pain in the abdomen and extremities lasting for about 12 hours with weekly occurrences over a period of 12 years Prior to that he had had migraine type headaches for 6 years

DISEASES OF THE UTERUS

The usual diseases of the uterus show themselves with either abnormal bleeding or abnormal discharge However there is one condition which may give no local symptoms and which may give rise to fever namely degeneration of fibroids

Considering the number of myomas which are seen at autopsy and in surgical specimens it is apparent that few give rise to fever However Wilson (*226*) described the case of a woman with a history of slight metrorrhagia which finally led to a diagnosis of degeneration of a small fibroid of the uterus as the cause of obscure fever

SUMMARY AND CONCLUSIONS

Today with the widespread use of antibiotics and other anti infective agents as well as agents such as cortisone which alter

the course of many infections and other disea es, the clinical picture of obscure or prolonged fever is often altered from the usual one In approaching the problem of diagnosis of pro longed fever it is well to have in mind the common groups of disorders as they are outlined in this monograph When any agent is used in a patient who has an obscure fever it is impor tant to observe the possible causes very carefully When pa tients respond favorably the diagnosis may remain obscure When patients fail to respond some such disorder as a resistant infection a tumor or a blood dyscrasia should be suspected It is well to remember that the infections that are still missed are not infrequently bacterial endocarditis multiple pulmonary infarcts tuberculosis and infections of the liver and kidney The tumors that may be the cause of prolonged fever are those of the lung pancreas liver and kidney Of the blood dys crasias the lymphomas play an important role

In more and more cases collagen disease is being recog nized as a cause of prolonged fever

A carefully planned program of investigation should be worked out in all cases of obscure fever

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